


REVIEW

Open Access



Mineral medicine: from traditional drugs to multifunctional delivery systems

Xiaoqing Zhong^{1,2†}, Zhenning Di^{1,2†}, Yuanxin Xu^{1,2†}, Qifan Liang^{1,2}, Kuanhan Feng^{1,2}, Yuting Zhang^{1,2}, Liuqing Di^{1,2*} and Ruoning Wang^{1,2*} 

Abstract

Mineral drugs are an important constituent of traditional Chinese medicine (TCM). Taking minerals that contain heavy metals as drugs is a very national characteristic part of TCM. However, the safety and scientific nature of mineral drugs are controversial owing to their heavy metals and strong toxicity. In 2000, the Food and Drug Administration (FDA) authorized arsenic trioxide (ATO) as first-line therapy for acute promyelocytic leukemia. This makes the development and utilization of mineral drugs become a research hotspot. The development of nanomedicine has found a great prospect of mineral drugs in nano-delivery carriers. And that will hold promise to address the numerous biological barriers facing mineral drug formulations. However, the studies on mineral drugs in the delivery system are few at present. There is also a lack of a detailed description of mineral drug delivery systems. In this review, the advanced strategies of mineral drug delivery systems in tumor therapy are summarized. In addition, the therapeutic advantages and research progress of novel mineral drug delivery systems are also discussed. Here, we hope that this will provide a useful reference for the design and application of new mineral drug delivery systems.

Keywords: Mineral drug, Traditional preparation, Novel drug delivery system, Active ingredient

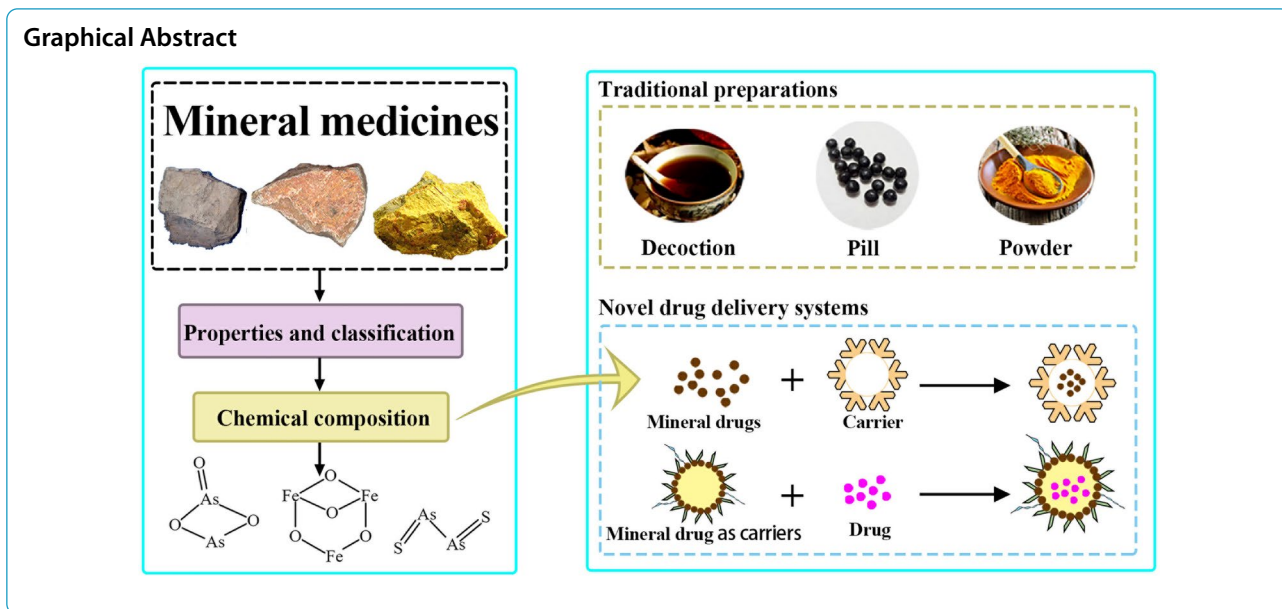
*Correspondence: diliuqing@njucm.edu.cn; ruoningw@njucm.edu.cn;
ruoningw@163.com

†Xiaoqing Zhong, Zhenning Di and Yuanxin Xu contributed equally to this work

¹ College of Pharmacy, Nanjing University of Chinese Medicine, Nanjing 210023, China

Full list of author information is available at the end of the article

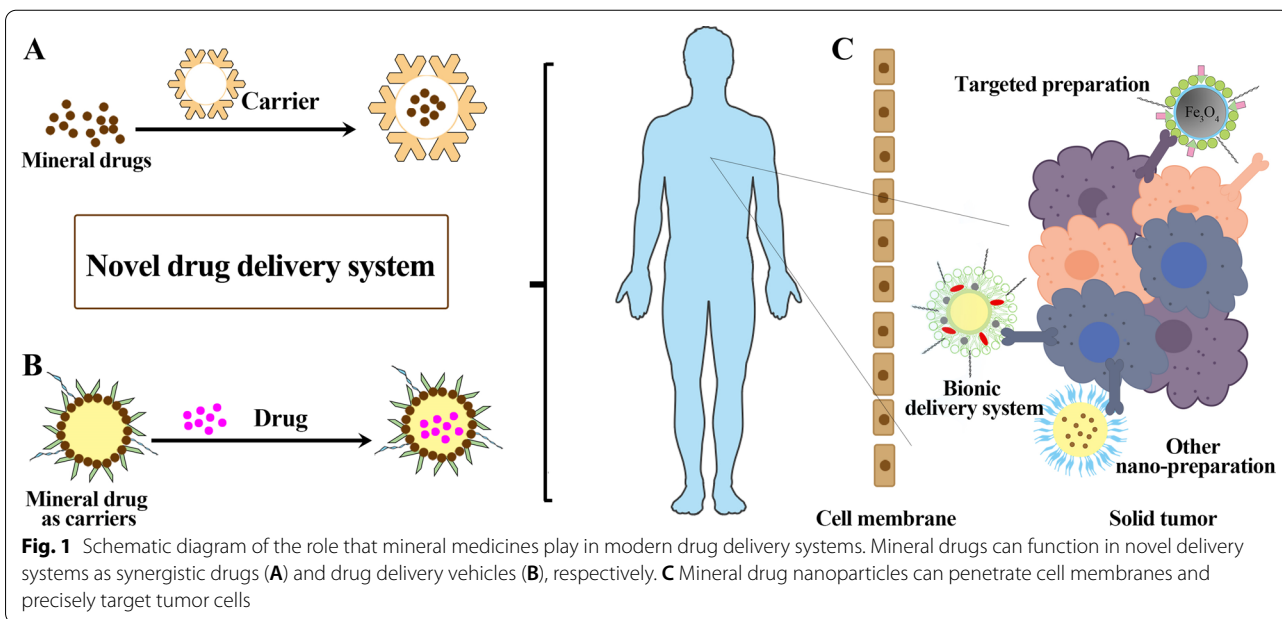




Background

Minerals are rich in resources in China and have significant curative effects as medicines, and are a unique component of traditional Chinese medicine (TCM). The research and utilization of mineral drug resources have a history of more than 2000 years. As early as the Spring–autumn Warring period, there were two kinds of mineral drugs used to treat diseases among the 122 kinds of drugs. Fifty-two disease prescriptions, the earliest existing medical classic, recorded the clinical application of

20 kinds of mineral drugs, such as realgar, cinnabar, and saltpeter. With the in-depth study of TCM, mineral medicine has gradually become a major research hotspot of drug development and application at home and abroad. Mineral medicine is a general term for natural minerals with medicinal value, mineral processed products and fossils of animals or animal bones. Among them, natural minerals such as cinnabar, gypsum, calamine, and ochre. The processed products of minerals include light powder, red powder, autumn stone and so on. Fossils of animals



or animal bones include keels, stone swallows, etc. [1–3]. Modern pharmacology found that many mineral drugs have a good curative effect for a variety of malignant tumors, such as arsenic and cinnabar. Yet, the practical trial of mineral drugs is curbed on account of the problems of inferior water solubility, high content of heavy metals, and severe toxicity. Recently, the research of some novel drug delivery techniques has brought opportunities for the development and adoption of mineral drugs.

Many studies focus on the drug delivery systems loaded mineral drugs, to acquire advanced efficacy and decreased toxicity with less adverse reactions. As shown in Fig. 1A, B, mineral drugs usually play a significant role in tumor therapy in the forms of drugs or carriers. Figure 1C shows that mineral drug nanoparticles can accurately penetrate the cell membrane to the tumor tissues. Ettliger et al. designed a kind of zeolitic imidazolate skeleton-8 as the pH-responsive messenger of arsenic trioxide (ATO), which has high remedy loading and significant pH triggered release behavior at the same time [1]. It has been proved to be a promising candidate material for transporting arsenic compounds. According to literature reports polylactic acid/magnetic compound nanoparticles, liposome complexes, amino acid, and other materials are used to deliver ATO to revamp the cure of arsenate in carcinoma treatment [2–4]. Another typical mineral drug is magnetite, which is mainly composed of Fe_3O_4 . Rayegan et al. loaded cephalixin (CPX) on magnetic nanoparticles encapsulated in basilicum seed mucilage (BSM) to prepare the complex with more gradual and sustained drug release ($\text{Fe}_3\text{O}_4@BSM\text{-CPX}$). With the help of magnetic targeting of Fe_3O_4 , a further drug send system was developed, and its antibacterial ability of the complex was significantly increased [5].

This review systematically summarizes the latest research on the enhancement of the curative effect of mineral drugs in the drug delivery system. Of note, the classification and active components of mineral drugs are introduced to promote the understanding of mineral drugs. More importantly, the modern pharmacological effects of mineral drugs are described in detail. Based on the active components and pharmacological activities of mineral drugs, the recent research progress of mineral drugs combined with novel drug delivery systems is highlighted. In the end, some critical challenges in the research of mineral drugs based on drug loading systems are discussed to provide a reference for the future development of mineral medicines.

Properties and classification of Chinese mineral medicine

Mineral drugs of TCM include original minerals (cinnabar, gypsum, calamine, etc.), processed products with minerals as raw materials (calomel, mirabilite, etc.),

fossils of animals, or animal bones (fossil fragments, dragon teeth, etc.). It is a part of the characteristics of Chinese medicine and has an idiographic function in the progress of TCM [6]. With the development of the internationalization of TCM, the research of traditional mineral medicines is gradually in-depth and extensive. In this section, we will outline the properties and classification of mineral drugs.

Mineral properties of Chinese medicine

Medicate with minerals, especially mineral medicine containing heavy metals, is a very extraordinary part of TCM. In the second century before Christ, mercury could be refined from cinnabar. In Song Dynasty, there are 139 kinds recorded in Zheng Lei Ben Cao and 222 kinds recruited in the Compendium of Materia Medica. Mineral drugs are abundant in resources and used widely. Figure 2 vividly shows the development of mineral medicine for thousands of years, indicating that mineral medicine has always been a part of TCM.

Except for a few natural elements, mineral drugs are mostly composed of a lot of compounds. Each mineral has certain physical and chemical properties. The knowledge of mineral medicine is generally identified from its appearance, physical and chemical properties, and microscopic observation. The appearance properties of mineral medicine include color, streaks, texture, smell, hardness, cleavage, fracture, magnetism, and specific gravity. Of note, the pyrite is dense, massive, and has green–black or red–brown streaks. Meanwhile, magnetite, commonly used in Chinese medicine for tranquilization, is gray–black, irregular block, metallic luster. Chlorite schist is greenish-black with glassy luster, and its cross-section is lamellar. Among them, mineral medicine has its inherent streak color. The streak color is the color of the powder trace left by the mineral after scratching on the white wool porcelain plate. The streak color may be different from the color of the mineral itself. For example, the surface of the pyritum is bright yellow, and the streak color is green–black to brown–red. In addition, microscopic identification can more accurately identify drugs from the optical properties of mineral drugs. At present, the identification of mineral medicines is gradually inclined to rely on various modern scientific and technological means, such as X-ray diffraction, electron microscopy, atomic absorption spectroscopy, thermal analysis, phase analysis, infrared spectroscopy, and nuclear magnetic resonance.

In recent years, the pharmacodynamic research of traditional Chinese medicine decoction has become more and more in-depth. Some studies believe that the metal ions in mineral medicines may participate in the formation of nanostructures of other ingredients

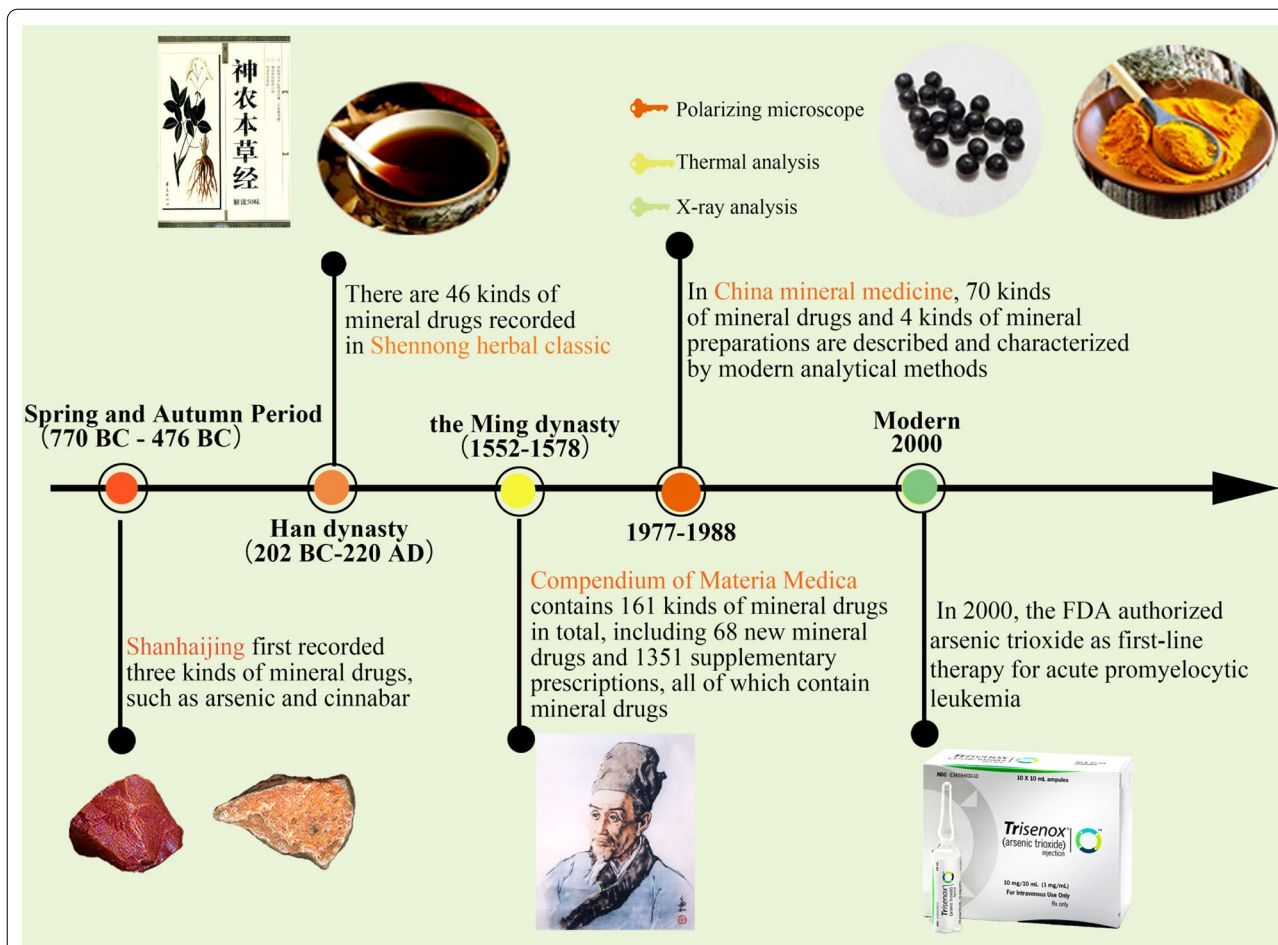


Fig. 2 Illustration of the development process of mineral pharmaceutical preparations. The application of mineral medicine was first recorded in “Shanhaijing”. “Shennong herbal classic” and “Compendium of Materia Medica” have sorted out the mineral medicines. In the twenty-first century, with the development of modern scientific and technological means, people’s understanding of mineral drugs has gradually deepened. The FDA’s first approval of arsenic trioxide as a first-line anticancer drug is of epoch-making significance. (The copyright of the pictures from network sources in the figure is shown below. Copyright© 2012–2021 Chengdu Gaoxin bingzhengtang TCM outpatient department Co., Ltd. all rights reserved. Copyright@2014 www.fl2j.com. Copyright© 2013 Phoenix New Media Limited All Rights Reserved. Copyright© 2019 www.tcmdoc.cn. Copyright© 2008–2013 gucn.com. Copyright© 2008 <https://www.zhihu.com/>. Copyright© <https://www.hrhnyy.cn/>. Copyright 1996–2006 Cerner Multum, Inc.)

in the decoction through coordination, forming self-assembled nanoparticles, thus exerting their medicinal effects. With the expansion of mineral drug research, many mineral nanoparticles have attracted extensive attention in the fields of bioengineering, biomedicine, and food analysis because of their unique properties [7]. For example, Fe_3O_4 nanoparticles have the properties of superparamagnetic, high external area, and low toxicity, which are widely used to enhance medication efficacy and improve cancer treatment effects in the magnetic targeted delivery systems [8, 9]. Table 1 summarizes the classification and efficacy indications of mineral drugs in TCM.

Common classification of mineral drugs

In traditional Chinese medicine theory, mineral medicines can be divided into five categories according to their properties and functions: sedation and tranquility, tourniquet hemostasis, detoxification, vigorous purification of drainage, and insecticide. For example, cinnabar and magnetite have a sedative effect, and ochre has a hemostatic effect. At present, the modern classification of mineral medicines is mostly classified according to the type of anion or cation that is the main component of the mineral. The Chinese Pharmacopoeia adopts anion classification. For example, cinnabar and realgar are sulfur compounds, gypsum and strange stone are sulfates,

Table 1 Summary of active components and pharmacological effects of mineral drugs

Compound	Source	Efficacy indications	Pharmacological activity and mechanism
Mercury	Cinnabar (HgS)	Tranquilization with heavy prescription, improving eyesight, and removing toxicity substances	Conserve dopaminergic neurons from lipopolysaccharide-induced neurotoxicity by suppressing the microglial activation and proinflammatory factor production [114] Neuroprotective effect on ischemic stroke and reperfusion injury [115] Neuroprotective effect on neurodegenerative diseases [116] Reduce oxidative stress by regulating 5-HT metabolism [126] Induce apoptosis of A549 lung adenocarcinoma cell line [127]
Iron	Magnetite (Fe ₃ O ₄) Ochre (Fe ₂ O ₃)	Tranquilization with heavy prescription and suppressing hyperactive liver and subsiding yang Suppressing hyperactive liver for descending adverse qi and cooling blood for hemostasis	Inhibit the expression of some inflammatory cytokines and interferon response genes, regulate T cell immune activity, and play an anti-inflammatory role [128] Induction of TNF in RAW264.7 cells- α and IL-6 expression [129, 130] Increase the utterance level of Aquaporin-3, accelerate the formation of collagen and capillaries on the wound, and promote the proliferation of granulation tissue, thereby promoting the healing of the skin wound [131, 132]
Calcium	Gypsum (CaSO ₄ ·2H ₂ O)	Clearing heat-fire and quenching thirst	Inhibit the proliferation of leukemia cell line F-36P and induce its apoptosis [133] Inducing apoptosis of human liver cancer HepG2, QGY-7703 cells and blocking cell cycle G2/M progression [134–137] Inhibit the overexpression of microRNA-372 to restrain the pervasion and diaspora of prostate neoplasm cells [138] Prohibition of gastric carcinoma cells metastasis via the NFA Tc3/c-Myc roadway [139, 140] Repress the activity of MCF-7 and MDA-MB-231 in human chest cancer cells [91, 141]
Arsenic	Realgar (As ₂ S ₃)	Killing ascarid and removing toxic substances, eliminating dampness and phlegm, and preventing malaria	Induce Molt-4 and Mutz-1 autophagy damage in leukemia cells [133]
Aluminum	Arsenic trioxide (As ₂ O ₃) Alum (KAl (SO ₄) ₂ · 12H ₂ O)	Eliminating pus and necrotic tissues, dissipating phlegm, and preventing malaria Killing ascarid and removing toxicity substance for external, eliminating phlegm for calming endogenous wind and hemostasis for internal	Reduce the content of collagen in the myometrium, gene representation, and albumin concentration of MMP-2 and MMP-9 to improve uterine leiomyoma [142]
Copper	Halloysite (Al ₄ (Si ₄ O ₁₀)(OH) ₈ · 4H ₂ O)	Astringing sores, promoting granulation and hemostasis	Protect locally inflamed gastrointestinal mucosa
Sodium	Blue vitriol (CuSO ₄ ·5H ₂ O) Mirabilite (Na ₂ SO ₄ · 10H ₂ O)	Eliminating necrosis and detoxication Clearing heat for detumescence and moistening dryness for relaxing bowels	Promote bile secretion and have a sialagogic effect Promote intestinal activity and improve gastrointestinal dysfunction [143]
Magnesium	Talc (Mg ₃ (Si ₄ O ₁₀)(OH) ₂)	Clearing heat and freeing strangury	Protect the inflamed gastrointestinal mucosa or damaged skin tissues [144]

calcium amines are carbonates, magnetite and ochre are oxides, and calcium amines are halides. Cation classifications include mercury compounds, arsenic compounds, lead compounds, iron compounds, calcium compounds, aluminum compounds, copper compounds, sodium compounds, and magnesium compounds [4, 5].

Chemical constituents of minerals in traditional Chinese medicine

Most mineral drugs are compounds containing heavy metal elements. The main ingredients include arsenic, lead, mercury, copper, iron, magnesium, aluminum, calcium, silicate, sulfate, and other ingredients. These ingredients include trace elements required by the human body and have an impact on human health, which has attracted wide attention from researchers.

Chemical composition and pharmacological action of mineral medicine

Many mineral drugs have significant pharmacological activity. Copper, iron, etc. are common metal elements and trace elements necessary for the human body. Lack of it can cause physiological dysfunction and cause disease. Copper has certain effects on cardiovascular, bone marrow, central nervous system, and red blood cell production. Copper participates in the body's biochemical functions such as oxidative phosphorylation, free radical detoxification, melanin synthesis, catecholamine metabolism, connective tissue cross-linking, blood coagulation, and hair formation. Azurite ore, chlorocopper ore, and bornite ore can all be used as medicine. $\text{CuSO}_4 \cdot 5\text{H}_2\text{O}$ is the main component of chalcogenide and has a good antibacterial effect. Studies have shown that, compared with ordinary copper oxide, nano-copper oxide has superior properties such as surface effect, quantum size effect, volume effect, and macroscopic quantum tunneling effect [10, 11]. Iron is the most abundant and important hematopoietic element in the human body. Iron-containing drugs mainly exist as iron elements, iron oxide, iron sulfide, or iron sulfate. Mineral drugs containing iron and its compounds are clinically used to treat convulsions, swelling toxins, iron-deficiency anemia, and various causes of blood deficiency and blood deficiency. Among them, magnetite mainly contains iron tetroxide, ochre mainly contains iron trioxide, and pyrite mainly contains iron disulfide. With the research of nanomedicine, magnetic nanoparticles have shown positive advantages in biomedicine and drug delivery [12–15].

Calcium and sodium are also common mineral medicine ingredients. Calcium-containing mineral medicines mainly contain oxides, carbonates, and calcium fluoride as their main active ingredients. Calcium-containing mineral drugs have a wide range of clinical applications

in gynecological diseases. In addition, calcium mineral medicine also has a special anti-convulsant and soothing effect and is clinically used for epileptic mania. For example, the main component of amethyst is CaF_2 , which can excite the central nervous system and ovarian secretion function. Sodium-containing mineral drugs are mainly used clinically to reduce local leukocyte infiltration, regulate body immunity, and prevent postoperative infections. For example, borax mainly contains sodium tetraborate, which has antiseptic and anticonvulsant effects. Glauber's salt mainly contains water-containing sodium sulfate, which has anti-inflammatory, anti-bacterial, and laxative effects.

Mineral medicine also contains non-metallic compounds, such as talc, white quartz, and other traditional Chinese medicines containing silicon. Talc is a silicate mineral, mainly containing hydrous magnesium silicate, which has the function of protecting skin and mucous membranes and antibacterial. The main component of white quartz is silica, which has sedative, calming, anti-tussive and anti-asthmatic effects. In addition, silica, the main component of the quartz photo album, can be used as a load-bearing coating for various nano-drugs, exaggerating the stability of the nano-particles and increasing the efficacy of the nano-particles [16–19].

Toxicity of mineral medicine

Some toxic heavy metals also have medicinal value, such as mineral medicines containing mercury, lead, gold, and silver. For example, cinnabar is a natural ore of mercury sulfide. HgS is a substance that is hardly soluble in water and organic solvents. Under the action of acid effect and complexing effect in the human body, it can dissociate and complex reaction with amino acid and other biological molecules to form complexes with strong physiological activity and less toxicity. Therefore, cinnabar can act on the central nervous system, with hypnotic, brain protection, anti-fear, anti-anxiety, and anti-convulsant effects. Realgar mainly contains arsenic sulfide, which is antibacterial and resistant to blood-sucking worms. The main component of arsenic is arsenic trioxide, which can be used to treat leukemia and inhibit tumor angiogenesis [6].

Mercury is a toxic metal commonly found in mineral medicines. Inorganic mercury, elemental mercury, and methylmercury have strong binding to human serum proteins, and interfere with cell metabolism by binding to sulfhydryl groups of receptor proteins or cellular enzymes, thereby inducing cell death. Mercury can accumulate in vital organs such as the liver, kidneys, brain and heart with blood circulation. Arsenic also has significant cytotoxicity, and arsenic oxide can specifically damage pyruvate dehydrogenase in

mitochondria, hindering both aerobic and anaerobic respiration. The cells thus suffer from acidosis and undergo rapid apoptosis. Long-term consumption of large amounts of realgar can produce obvious toxic reactions. One of the mechanisms responsible for the nephrotoxicity of realgar may be the accumulation of renal copper. However, there are also clinical methods for treating malignant diseases by inducing rapid apoptosis of cells.

Since the safety of toxic mineral drugs has always been controversial, there have been many cases of oral or topical poisoning of mineral drugs at home and abroad. Therefore, the Pharmacopoeia of the People's Republic of China has strict regulations on the use of toxic mineral drugs. For example, the incidence of adverse reactions caused by cinnabar increases with the increase of the dosage and the prolongation of the medication time. Therefore, cinnabar should not be taken in large quantities or a small amount for a long time, 0.1–0.5 g per day, mostly in pills and powder, not in decoctions, and appropriate for external use. The light powder should not be used in excess. It should be used with caution for internal use and appropriate amount for external use. In addition, it is also necessary to formulate corresponding drug restrictions for specific groups, such as pregnant women, children, etc., should pay attention to the contraindications and limits when using toxic mineral drugs.

The minerals of most Chinese medicines contain a mixture of many heavy metal elements. Most metal mineral drugs are hard in texture and difficult to be crushed into medicines. Therefore, they are usually processed by methods such as high-temperature calcination, the addition of auxiliary materials, grinding, water jetting, and purification before clinical application. The processing steps can also reduce the side effects of toxic mineral drugs. The composition and content of mineral medicines processed from the same mineral raw materials are different, which will lead to changes in their pharmacological effects. For example, the main component of gypsum is $\text{CaSO}_4 \cdot 2\text{H}_2\text{O}$, which has a strong heat-clearing and clearing ability, while forged gypsum mainly contains calcium sulfate, which has a stronger hemostatic effect. The iron-containing mineral drug substitute ocher is calcined and quenched with vinegar to make the texture crisp and easy to crush. Among them, the content of toxic metals such as arsenic, lead, and mercury is significantly reduced, while the dissolution of iron, calcium, magnesium and other elements is significantly increased. The acute toxicity of realgar processed with yogurt was significantly reduced, but its analgesic and anti-inflammatory effects were the same as those of the raw product [7–9].

Discussion on traditional preparations of mineral drugs

The medicament forms of TCM are an extremely characteristic part of the Chinese medicine culture. Meanwhile, it is also the product of TCM syndrome differentiation theory. The dosage forms of drugs always change with the nature of ailments and the physicochemical properties of the mineral drugs themselves. The great majority of mineral drugs are heavy and venomous. In traditional applications, most of them are prepared into pills, soups, and powders for the treatment of some difficult and miscellaneous diseases. Starting from the traditional dosage forms of TCM, this section discusses the application of mineral drugs in traditional medicine prescriptions and patent medicines. Table 2 shows detailed information on traditional mineral preparations.

Traditional decoction of mineral medicine

The most scripture and oldest form of TCM is decoction. It has the characteristics of high-speed absorption and swift function. Mineral drugs are usually decocted with the pattern of pre-frying to fully stimulate the active ingredients. The reason is that most of the minerals are hard to dissolve or contain certain toxicity. Moreover, since the longtime of decocting, it can greatly reduce the toxicity. Baihu decoction (BHD) has the effect of clearing away heat and promoting body fluid with the gypsum as its sovereign drug. Modern research demonstrates that the material foundation of BHD is calcium ion in gypsum, in which 83.25% Ca exists in the free state and 23.79% Ca retains in soluble filtrate in the organic form [20]. By reducing the levels of interleukin-1 β (IL-1 β) and tumor necrosis factor α (TNF- α) in serum and hypothalamus of rabbits which was injected lipopolysaccharide, the BHD has an obvious antipyretic effect [21]. Therefore, BHD can become a natural anti-fever and anti-inflammatory candidate. BHD is diffusely used in the clinic to heal infectious diseases, viral poor and high fever, acute cerebral hemorrhage, diabetes, acute hyperglycemia, and rheumatoid arthritis [22, 23]. As shown in Table 2, Dachengqi decoction (DCQD) is a classical Chinese medicine recipe for curing constipation with excess heat. Mirabilite is one of the significant minister medicines, with positive heat-clearing and catharsis effects [24]. DCQD is constantly used in clinical therapy of acute cholecystitis, acute appendicitis, acute simple intestinal obstruction, and so on. It is reported that DCQD contributed with conventional therapy has a significant effect in the curing of hyperlipidemia acute pancreatitis [25]. Network pharmacology research found that DCQD on the therapeutics of pancreatitis may be achieved via two-way regulation, including anti-inflammatory and antioxidant effects, pro-apoptosis, and regulation of pancreatic secretion. This process involves numerous

Table 2 A summary of traditional preparations of mineral drugs

Preparation	Chinese patent medicine	Mineral medicines	Pharmacological action	Clinical application
Decoction	Baihu decoction	Gypsum	Clearing heat and promoting fluid production	Viral cold high fever, acute cerebral hemorrhage, infectious diseases, etc
	Zhengan Xifeng decoction	Os Draconis	Suppressing hyperactive liver for calming endogenous wind and nourishing yin for suppressing hyperactive yang	Hypertension, cerebrovascular disease, chronic gastritis, intractable insomnia, etc
	Dachengqi decoction	Mirabilite	Completed under the hot junction	Simple intestinal obstruction, adhesive intestinal obstruction, acute cholecystitis, acute pancreatitis, etc
	Bixie Shenshi decoction	Talc	Clearing heat and cooling blood and promoting diuresis	Gout, mycotic vaginitis, acute eczema, erythema nodosum, lower limb erysipelas
	Cream soup	Os Draconis	Relieving diarrhea with astringents	Chyluria, etc
	Chishizhi Yuyuliang decoction	Halloysite, Limonite	Astringing the intestine and arresting proptosis	Diarrhea, functional uterine bleeding, chronic enteritis, metrorrhagia, etc
	Guizhi Gancao Longgu Muli decoction	Os Draconis	Anti-depression, amelioration of menopausal syndrome	Insomnia, spontaneous sweating, night sweats, etc
	Jianling decoction	Ochre, Os Draconis	Nourishing yin for tranquilization and suppressing hyperactive liver for calming endogenous wind	Hypertension, cardiac neurosis hemorrhagic sinusitis, migraine, intractable hiccup, etc
	Ephedra Almond Licorice Plaster decoction	Gypsum	Antiviral, antipyretic, antitussive, expectorant, diuretic, sedative et al	Community-acquired pneumonia, pediatric acute bronchopneumonia, etc
	Zhuling decoction	Talc	Diuretic, antibacterial, improve renal function, inhibit the formation of kidney stones	Recurrent urinary tract infection, ascites due to hepatitis B cirrhosis, brain injury, etc
	Daqinjiao decoction	Gypsum	Anti-inflammatory	Gout, rheumatoid arthritis, facial palsy, scapulo-humeral periarthritis, etc
	Xuanbai Chengqi decoction	Gypsum	Ventilating lung qi for dissipating phlegm and purgation	Pulmonary heart disease, asthma, bronchiectasis, lung abscess, etc
	Dahuang Mudan decoction	Mirabilite	Clearing heat for detumescence	Acute simple appendicitis, pelvic inflammation
	Xuanfu Daizhe decoction	Ochre	Harmonizing stomach for descending adverse qi	Gastritis, gastric distension, pyloric insufficiency, nervous hiccup, etc
	Huanglong decoction	Mirabilite	Clearing intestinal heat, replenishing qi, and nourishing blood	Typhoid fever, epidemic cerebrospinal meningitis, senile intestinal obstruction, etc
Pill	Jiebiao Zhuifeng pills	Cinnabar, Realgar	Dispel wind and dispel exterior, strengthen stomach and balance	Headache with wind-cold and cough
	Fangfeng Tongsheng pills	Mirabilite, Talc, Gypsum	Relieving superficials and catharsis and clearing heat and removing toxicity	Cold, trigeminal neuralgia, acute shigellosis, acute conjunctivitis, etc
	Niuhuang Qingwei pills	Gypsum	Improve gastrointestinal function and has a certain analgesic effect	Tonsillitis, gingivitis, recurrent oral ulcers, acute pharyngitis
	Niuhuangzhibao pills	Gypsum, Mirabilite, Realgar	Clearing heat-fire and facilitating feces excretion	Functional constipation

Table 2 (continued)

Preparation	Chinese patent medicine	Mineral medicines	Pharmacological action	Clinical application
	Liushen pills	Realgar	Antibacterial, anti-inflammatory, anti-viral, anti-convulsive, sedative, and enhance immunity	Chronic pharyngitis, chronic hepatitis, upper gastrointestinal cancer, leukemia, etc
	Jiuzhi Qingxin pills	Cinnabar, Realgar	Clearing heat-fire and facilitating feces excretion	Dizziness, mouth and nose sores, sore throat, constipation knots, etc
	Liangge pills	Gypsum, Mirabilite	Anti-inflammatory and antipyretic	Sore mouth and tongue, hematemesis, cough, sore throat, etc
	Qingwei Huangliang pills	Gypsum	Antipyretic, anti-inflammatory, anti-viral	Stomatitis, periodontitis, and oral ulcer
	Huanglian Shangqing pills	Gypsum	Antipyretic, anti-inflammatory, antiviral, analgesic	Acute stomatitis, acute conjunctivitis, acute gastroenteritis, toothache mouth ulcer, etc
	Fufang Niu Huang Qingwei pills	Gypsum, Mirabilite	Antipyretic, anti-inflammatory, and anti-viral	Acute pharyngitis, tonsillitis, oral ulcer, and periodontitis
	Daochi pills	Talc	Antibacterial, anti-inflammatory, analgesic, diuretic, antipyretic, anti-platelet aggregation, hemostasis	Stomatitis, urethritis, acute and chronic pyelonephritis, urinary calculi
	Jinsuo Gujing pills	Os Draconis	Decrease urine protein, regulate blood lipid and improve pathological changes of renal tissue	Male neurosis effects, chronic cervicitis, intractable night sweats, etc
	Wan's Niu Huang Qingxin pills	Cinnabar	Clearing away the heat-evil and calming down	Japanese encephalitis, pertussis complicated with meningoencephalitis, etc
	Niu Huang Qingxin pills	Cinnabar, Realgar	Sedation, anti-convulsion, antipyretic, antihypertensive, improve hypoxia tolerance	Severe amnesia, aphthous stomatitis, intractable hiccups
	Angong Niu Huang pills	Cinnabar, Realgar	A calm, strong heart, protect brain tissue, antipyretic, anti-inflammatory, anti-pathogenic microorganisms	Japanese encephalitis, toxic pneumonia, high fever and coma caused by infection or poisoning, etc
	Suhexiang pills	Cinnabar	Dilate coronary artery, increase coronary flow, slow heart rate, reduce myocardial oxygen consumption, etc	Coronary heart disease angina, myocardial infarction, acute cerebrovascular disease, epilepsy, etc
	Mengshi Guntan pills	Mica-schist	Dispelling phlegm, relieving asthma and sedation, etc	Stroke, schizophrenia, epilepsy, migraines, neurosis effects
	Medical pills	Cinnabar, Realgar, Alum	Sedation, analgesia, anticonvulsants, etc	Epilepsy, manic psychosis
	Baizi Yangxin pills	Cinnabar	Inhibit the central nervous and play sedation, hypnosis, diazepam, anti-convulsion	Neurasthenia, memory loss, schizophrenia, menopause, hyperthyroidism, heart disease, etc
	Cizhu pills	Magnetite, Cinnabar	Nourishing blood for improving eyesight and tranquilization	For epilepsy, tinnitus, insomnia, and so on
	Tianwang Buxin pills	Cinnabar	Anti-myocardial infarction, enhance the body's immune function, sedation, anti-convulsion, anti-arrhythmia, etc	Low blood pressure, insomnia, psychosis, hyperthyroidism, climacteric syndrome, chronic conjunctivitis, myocarditis, tuberculosis, hypertension, etc
	Zhusha Anshen pills	Cinnabar	Sedative-hypnotic, antiarrhythmic, anticonvulsant, antipyretic and analgesic, etc	Neurasthenia, schizophrenia, epilepsy, myocarditis, etc

Table 2 (continued)

Preparation	Chinese patent medicine	Mineral medicines	Pharmacological action	Clinical application
	Naoliqing pills	Magnetite, Ochre	Lower blood pressure, sedation, antiemetic, vasodilator, etc	High blood pressure, arteriosclerosis, etc
	Zaizao pills	Cinnabar	Anti-coagulation, improve microcirculation, anti-inflammation, etc	Stroke, hemiplegia, numbness of hands and feet, pain and convulsion, etc
	Geije Dingchuan pills	Gypsum	Antitussive, expectorant, anti-asthmatic, anti-inflammatory, antibacterial, enhance immune function	Bronchitis, asthma, tuberculosis, etc
	Suoyang Gujing pills	Os Draconis, Halite	Treatment of kidney deficiency	Male sexual neurosis effects, prostatitis, infertility, etc
	Shixiang Fansheng pills	Cinnabar, Mica-schist	Dissipating phlegm for resuscitation and tranquilization	Hysteria, neurosis effects, shock, epilepsy, schizophrenia, depression, seizures, etc
Powder	Liuyi powder	Talc	Clear away heat and facilitate urination	Heat and dampness caused by fever, external treatment of prickly heat, etc
	Qili powder	Cinnabar	Remove stasis and detumescence, relieve pain and stop bleeding	Soft tissue injury, and other infectious, purulent diseases, etc
	Zixue powder	Gypsum, Talc, Magnetite, Cinnabar, Mirabilite, North Calcium	Antipyretic, anticonvulsant, sedative, antibacterial, anti-inflammatory	Japanese encephalitis, sepsis, acute zinc phosphide poisoning, etc
	Biwen powder	Cinnabar	Get rid of the heat and the pain	Summer heat stroke, motion sickness, seasickness
	Bingpeng powder	Cinnabar, Borax, Sodium sulfate powder	Anti-inflammatory, anti-fungal, analgesic, etc	Gingival swelling and pain, tonsillitis, oral ulcers, mumps, herpes zoster, fungal vaginitis, and cervical erosion

pathways and signals, such as interleukin-17 (IL-17), tumor necrosis factor (TNF), and nuclear factor kappa B, but the concrete mechanism of DCQD needs further study [26–28]. In clinical application, DCQD also illustrates the superiority in treating apoplexy, cerebral hemorrhage, and other diseases. From 296 active components of DCQD, 52 linchpin elements related to stroke were selected, which are mainly involved in the regulation of oxidative stress, lipid metabolism, and anti-inflammation [29]. Zeng et al. treated intracerebral hemorrhage model rats with DCQD for 7 days and found that the number of M2 microglia and N-methyl-D-aspartate receptors in the DCQD group increased significantly through the behavior test and protein subcomponent analysis. In this regard, the authors suggest that the mechanism may be through inhibiting mitogen-activated protein kinase and activating M2 microglia to protect rats with cerebral hemorrhage [30].

Prescription preparation of mineral medicine

Based on the boundedness of clinical application of decoction, pills play an important role in mineral drug preparations. The reason is the easy storage, long efficacy, and convenient use of pills. The great majority of pills are designed for the therapeutics of some chronic and debilitating diseases, such as Zhusha Anshen pills containing HgS, Cizhu pills containing Fe_3O_4 , etc. And they all possess the characteristics of slow absorption, lasting curative effect, for epilepsy, insomnia, tinnitus has a superior therapeutic effect. Some of the pills prepared from certain aromatic or toxic minerals can also make it in fast treatment, such as Angong Niu Huang pills and Suhexiang pills. Suhexiang pills, which are mainly composed of cinnabar, have a positive protective effect on the acute ischemic lesion of myocardial cells. It has been found that the Suhexiang pill can dilate coronary arteries and reduce myocardial oxygen consumption [31]. Spontaneously, it is commonly used in the clinical treatment of coronary heart disease angina pectoris, myocardial infarction, and other emergencies. With the discovery of a novel drug matrix, pills have shown great potential in sustained-release and controlled-release preparations. Rational platform design can maximize the efficacy of mineral drugs and minimize their adverse effects.

The powder is divided into external and internal use of two, mineral medicine oral powder is generally developed into a certain size of dust and taken with water or decoction. The powder has the virtues of both decoction and pills, which have high-speed absorption and rapid activity. For some powerful and mostly toxic mineral drugs, the oral powder is generally used in some emergency treatment, and there are strict dosage restrictions. For example, the dosage of HgS cannot exceed 0.5 g, and

As_2S_2 cannot outstrip 0.1 g. Zixue, a powder with excellent clinical curative effect, contains a large number of minerals, including gypsum, north calcitum, talc, magnetite, mirabilite, cinnabar, etc. Modern research shows that it has antipyretic, anticonvulsant, sedative, antibacterial, anti-inflammatory, and other effects, and represents excellent results in the treatment of Japanese encephalitis, epidemic cerebrospinal meningitis, sepsis, and other acute diseases. Qili powder is another typical mineral powder preparation, and cinnabar is one of the eventful components. Qili powder has the functions of removing blood stasis, detumescence, relieving pain, and hemostasis. It is commonly used in soft tissue injury, fracture, and other diseases. Consult with the traditional dosage forms of mineral drugs can provide research direction and ideas for the modern development of mineral drugs.

Research on mineral drug delivery systems

The development of nano-drug delivery systems conducts opportunities for the growth and research of TCM, especially the application of mineral drugs. And it cannot be ignored, and always has the significance of TCM in the diagnosis and treatment of diseases. Exploration of active components and pharmacological effects of mineral drugs has always been the focus of scholars' research. Accordingly, there are a few studies on the delivery system of mineral drugs. Modern pharmacological studies have shown that mineral drugs such as arsenic trioxide and realgar have an active therapeutic effect on a variety of malignancies, including acute promyelocytic leukemia (APL), liver cancer, gastric cancer, and cervical carcinoma (Fig. 3), as shown in Table 3. Therefore, the research of mineral drugs in modern drug delivery systems is discussed in detail in this section. Firstly, the research of mineral drug delivery in nano-drug delivery was discussed from the aspects of APL, hepatocellular carcinoma (HCC), and other diseases. Then, taking magnetite as an example, the application of mineral drugs as carriers in the study of drug delivery systems is discussed.

Application of mineral drugs in tumor remedy

Acute promyelocytic leukemia

Acute promyelocytic leukemia is a common malignant disease of hematopoietic tissue. T (15, 17) chromosome rearrangements lead to this malignant tumor. APL is characterized by representative promyelocytic leukemia protein/retinoic acid receptor a gene fusion and high invasiveness and infiltration in clinical practice [32–35]. The oncogenic protein produced by the fusion can antagonize myeloid differentiation and promote APL to initiate cell self-renewal, leading to abnormal development of promyelocytic bone marrow infiltration [36, 37]. Owing to high early mortality, high recurrence rate, low survival



Fig. 3 Schematic illustration showing the pharmacological activity of mineral drugs and their advantages in tumor treatment. (The copyright of the pictures from network sources in the figure is shown below. Copyright© 2021 Sohu All Rights Reserved. Copyright© 1997–2021 <https://www.163.com/>.)

rate, and coagulopathy. It was once considered to be the most rapidly fatal leukemia [32]. Although all-trans retinoic acid (ATRA) and anthraquinone chemotherapy are recognized as effective therapies for APL, their side effects such as cardiotoxicity cannot be ignored [38]. Therefore, scientists are always devoted to finding ways to validly remedy APL. In the past 60 years, significant progress has been made in the treatment of APL. The introduction of ATO holds promise for the treatment of APL.

Arsenic has always been regarded as the king of poisons. However, its active ingredient ATO has recently been considered as one of the most effective drugs for the treatment of APL. As early as the 19th and early twentieth centuries, Western doctors found that arsenic had special effects in the treatment of leukemia, and adopted a variety of treatment methods such as oral, rectal, intramuscular and intravenous administration. Arsenic trioxide has been widely used in the world since the 1990s to treat acute promyelocytic leukemia. It is an original

invention of Chinese and Western medicine experts from Harbin Medical University in China. The use of hemoglobin can show extraordinary binding force with exogenous drugs, so that trivalent arsenic can be combined with hemoglobin. In addition, tumor cells will absorb nutrients preferentially to normal cells in the tissue, so that trivalent arsenic is mainly absorbed by tumor cells. destroy tumor cells. In addition, hemoglobin has the advantages of low cost, complete biocompatibility, and easy genetic engineering, all of which make hemoglobin an ideal drug delivery material. Fan et al. designed nanoparticles composed of polyethylene glycol (PEG), retinoic acid (RA), and 2-chloro-1,3,2-dioxarsolane (PEG-As-RA), which exhibited superior water solubility, stability, and biocompatibility [39]. Zhang et al. developed an ATO multifunctional drug delivery system based on a pH-low insertion peptide modification, which is termed as MnAs@SiO₂-pHLIP (Fig. 4A). Figure 4B, C, F illustrate that arsenical and manganese ions can aggregate efficiently in cancer cells. This drug delivery system can

Table 3 Novel preparations of mineral drugs and preclinical study

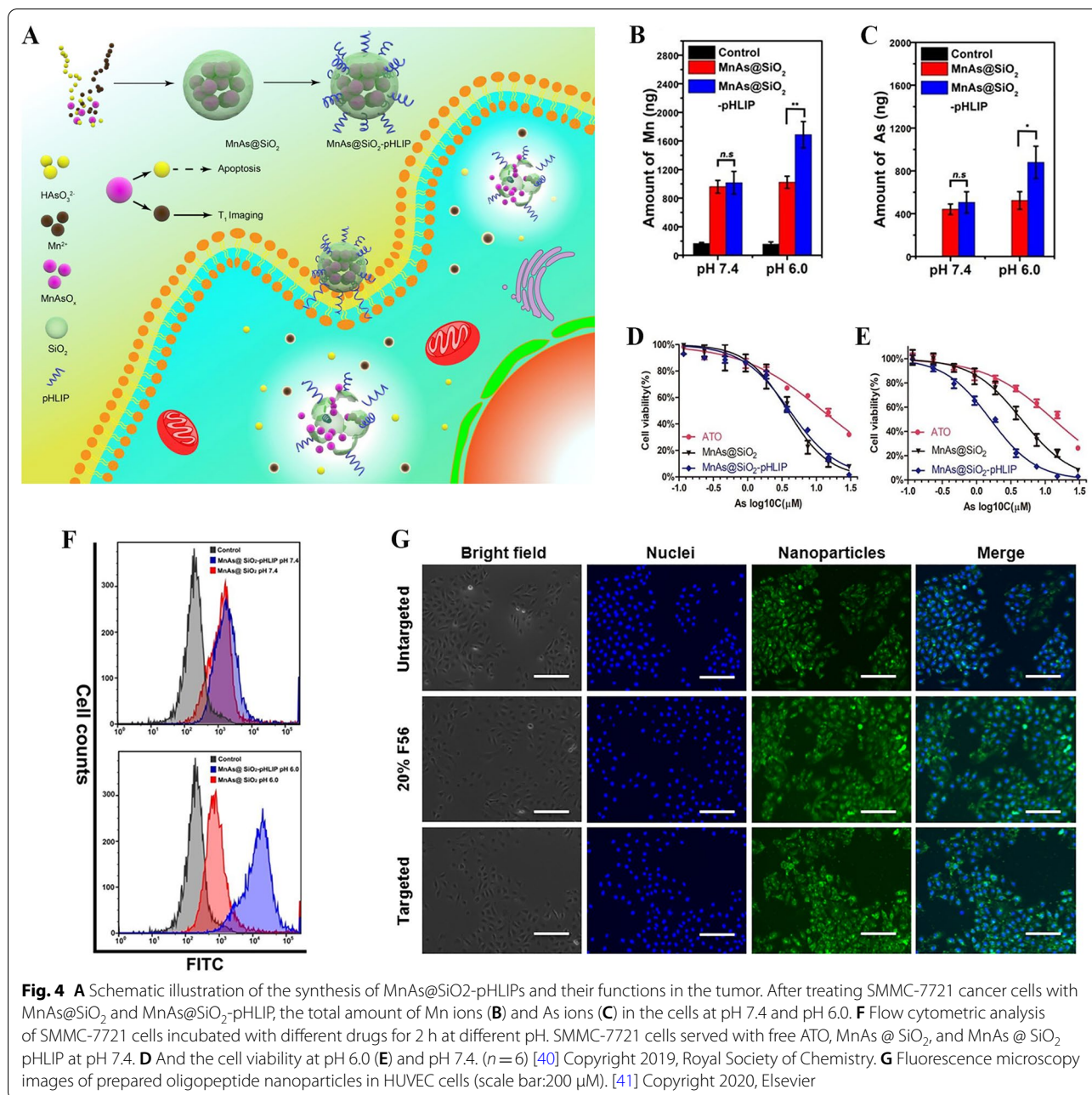
Register number	Study title	Conditions	Interventions/drugs	Locations
NCT04687176	Frontline oral arsenic trioxide for APL	APL	Drug: oral arsenic trioxide formulation	The University of Hong Kong
NCT03624270	Oral arsenic trioxide for newly diagnosed acute promyelocytic	APL	Drug: oral arsenic trioxide, all-trans retinoic acid, and ascorbic acid	The University of Hong Kong
NCT04689815	Oral arsenic trioxide for nucleophosmin 1 mutated acute myeloid leukemia (AML)	AML	Drug: oral arsenic trioxide formulation	The University of Hong Kong
NCT04634838	Efficacy dressings with copper oxide	Pressure ulcer	Device: medcu antibacterial wound dressings with copper oxide	Loewenstein Rehabilitation Center ra'anana, Israel
NCT01565798	Efficacy of copper to reduce acquisition of microbes and healthcare-acquired infections	Healthcare-acquired infection	Other: copper-alloy surfaced patient care objects	Medical University of South Carolina
NCT01678612	Efficacy of copper in reducing health-acquired infections in a pediatric intensive care unit	Nosocomial infections	Copper-alloy surfaced objects	Hospital Roberto del Rio, Santiago, Chile
NCT03323346	Phase II trial of disulfiram with copper in metastatic breast cancer	Breast neoplasm female	Drug: disulfiram	University hospital Olomouc, Olomouc, Czechia
NCT03284749	Effect of copper on the healing of obstetric wounds	Cesarean section and infection	Other: copper impregnated wound dressing, and normal wound dressing	Croydon health services NHS trust
NCT04511468	Zinc, chromium, vitamin C, and copper combination supplement for prediabetes progression	Prediabetes	Dietary supplement: zinc, chromium, vitamin C, and copper supplementation, and placebo	Human Nutrition Research Center
NCT01777919	Disulfiram/copper combination in the treatment of newly diagnosed glioblastoma multiforme	Glioblastoma multiforme	Temozolomide, disulfiram, copper	Olympion medical Center, Patras, Greece
NCT00608946	Treatment with copper in patients with mild Alzheimer's dementia	Alzheimer's disease	Dietary supplement: copper	
NCT03736109	Role of a copper-albumin complex in the treatment of knee osteoarthritis in human	Osteo arthritis knee	Genetic: soluble and genetic biomarkers measurements	
NCT02715609	Disulfiram/copper with concurrent radiation therapy and temozolomide in patients with newly diagnosed glioblastoma	Glioblastoma multiforme	Drug: disulfiram, and copper gluconate	Washington University school of medicine, Saint Louis, Missouri, United States
NCT01017315	Efficacy of baby talcum in the prevention of pruritus associated with cast	Fracture distal radius	Drug: baby talcum	Prince of Songkhla university
NCT04792970	Randomized controlled trial of talc instillation in addition to daily drainage through a tunneled pleural catheter to improve rates of outpatient pleurodesis in patients with malignant pleural	Malignant pleural effusion	Drug: talc	Duke University Medical center, Durham, North Carolina, United States
NCT00789087	Talc pleurodesis in patients with recurrent malignant pleural effusion	Recurrent malignant pleural effusion	Procedure: video thoroscopic talc poudrage, and talc slurry through a chest tube	University of são Paulo medical school
NCT03635138	Effect of the incorporation of copper and zinc nanoparticles into dental adhesives	Caries, dental	Other: metal nanoparticles (Zn and Cu), and dental adhesive pure	Eduardo Fernández G, Santiago, Metropolitana

Table 3 (continued)

Register number	Study title	Conditions	Interventions/drugs	Locations
NCT0475238	Effect of metallic nanoparticles on nosocomial bacteria	Nosocomial infections	Other: silver nanoparticles, and copper nanoparticles	Faculty of medicine-sohag University, Sohag, Egypt
NCT02200978	A study for improving the outcome of childhood acute promyeloid leukemia	Childhood acute promyelocytic leukemia	Drug: indigo naturalis formula, and ATO, ATRA (and 5 more...)	The first affiliated hospital of Sun Yat-Sen University
NCT044489706	Arsenic trioxide in recurrent and metastatic ovarian cancer and endometrial cancer with P53 mutation	Ovarian cancer	Drug: arsenic trioxide for injection	Shanghai Jiaotong university school of medicine affiliated rujin hospital
NCT02966301	Treatment of chronic graft versus host disease with arsenic trioxide	Chronic graft-versus-host disease	Drug: arsenic trioxide injectable solution	CHU de caen-institut d'Hématologie de basse normandie
NCT01470248	Study of arsenic trioxide in small cell lung cancer	Lung cancer	Drug: arsenic trioxide	Emory University Winship Cancer institute
NCT01791894	Arsenic trioxide in treating patients with basal cell carcinoma	Basal cell carcinoma of the skin	Drug: arsenic trioxide	Stanford university medical center
NCT03751917	Long-term safety study of arsenic trioxide in newly diagnosed, low-to-intermediate risk acute promyelocytic leukemia	Acute promyelocytic leukemia	Drug: Arsenic Trioxide	Aon Ss, Antonio E Biagio E.C. Arrigo-Alessandria-soc ematologia,Alessandria, Italy
NCT00009867	Arsenic trioxide in treating patients with urothelial cancer	Recurrent transitional cell cancer of the renal pelvis and ureter	Drug: arsenic trioxide	Cancer and leukemia group B
NCT00024258	Arsenic trioxide in treating patients with advanced neuroblastoma or other childhood solid tumors	Brain and central nervous system tumors	Drug: arsenic trioxide	Memorial Sloan-Kettering Cancer Center, New York
NCT00008697	Arsenic trioxide in treating patients with refractory or recurrent acute promyelocytic leukemia	Leukemia	Drug: arsenic trioxide	Washington university school of medicine
NCT00045565	Arsenic trioxide plus radiation therapy in treating patients with newly diagnosed malignant glioma	Adult giant cell glioblastoma	Drug: arsenic trioxide	New approaches to brain tumor therapy consortium, Baltimore
NCT00517712	Single-agent arsenic trioxide in the treatment of newly diagnosed acute promyelocytic leukemia	Acute promyelocytic leukemia	Drug: single-agent arsenic trioxide	Kidwai memorial institute of oncology, India
NCT00053222	Arsenic trioxide in treating patients with pancreatic cancer that has not responded to gemcitabine	Pancreatic cancer	Drug: arsenic trioxide	Decatur memorial hospital cancer care institute, Decatur, Illinois, United States
NCT00193518	Arsenic trioxide in relapsed/refractory chronic lymphocytic leukemia/small lymphocytic lymphoma	Chronic lymphocytic leukemia	Drug: arsenic trioxide	Tennessee Oncology, Nashville, Tennessee, United States
NCT00128596	Arsenic trioxide in treating patients with metastatic liver cancer that cannot be removed by surgery	Liver cancer	Drug: arsenic trioxide	UPMC cancer centers, Pittsburgh, Pennsylvania, United States

Table 3 (continued)

Register number	Study title	Conditions	Interventions/drugs	Locations
NCT00003630	Arsenic trioxide in treating patients with advanced solid tumors	Unspecified adult solid tumor, protocol-specific	Drug: arsenic trioxide	Memorial Sloan-Kettering cancer center, New York
NCT00075426	Arsenic trioxide in treating patients with locally advanced or metastatic non-small cell lung cancer	Lung cancer	Drug: arsenic trioxide	University of Texas medical branch
NCT00005069	Arsenic trioxide in treating patients with metastatic kidney cancer	Kidney cancer	Drug: arsenic trioxide	Memorial Sloan-Kettering cancer center New York
NCT00005040	Arsenic trioxide in treating patients with relapsed or refractory non-Hodgkin's lymphoma	Lymphoma	Drug: arsenic trioxide	Memorial Sloan-Kettering cancer center New York
NCT00036842	Arsenic trioxide in treating men with germ cell cancer	Extragenadal germ cell tumor testicular germ cell tumor	Drug: arsenic trioxide	MBCCOP-Gulf coast mobile, Alabama, United States
NCT03503864	Phase II study of combined chemotherapy with arsenic trioxide in stage 4/M neuroblastoma	Neuroblastoma	Drug: arsenic trioxide	Sun Yat-sen memorial hospital, Sun Yat-sen University
NCT04869475	Arsenic trioxide in refractory solid tumors with rescuable p53 mutation	Refractory solid tumors	Drug: arsenic trioxide	Department of Oncology, Ruijin hospital
NCT00621023	Cephalon decitabine, arsenic trioxide, and ascorbic acid for myelodysplastic syndrome	Myelodysplastic syndrome	Drug: decitabine, arsenic trioxide, and ascorbic acid	Duke university medical center



controllably release loaded ATO in response to an acidic environment, thereby promoting the apoptosis of cancer cells in Fig. 4D, E [40]. The application of protein peptides provides an efficient platform for the delivery of ATO. Fan et al. showed that double oligopeptide nanoparticles based on the principle of reverse micelles can significantly increase the loading rate and stability of ATO (Fig. 4G). This bone marrow targeted drug delivery strategy may be utilized to treat chronic myeloid leukemia and other hematological malignancies originating

from bone marrow [41]. Zn-based metal–organic framework zeolitic imidazolate framework-8 has proved to be a suitable candidate material for transporting arsenic compounds, which could not only enhance the transportation of ATO but also possess pH-responsive release capability [1]. Otherwise, Jin et al. loaded arsenite into liposomes (LIP) by electrostatic interaction with manganese ion to construct liposome-encapsulated arsenic manganese complex (LIP@MnAs_x). The research results show that LIP@MnAs_x is a desired arsenic-based nano-drug

system, which can improve the non-specific distribution of NaAsO₂ in the body [2]. These all provide us with ideas for delivering ATO to treat APL.

Glioma

Glioma is the most common primary intracranial disease with invasiveness growth, poor prognosis, high recurrence rate, and high mortality [42]. Multi-mode therapy such as chemotherapy, radiotherapy, and surgical resection are the main choices for the treatment of gliomas [43, 44]. However, the emergence of drug resistance and the presence of blood–brain barriers (BBB) continue to be problems impeding the mission of drugs. At the same time, the application of drug chemotherapy often generates irreversible damage to the body, and patients are usually accompanied by severe adverse reactions and pain. In addition, after brain surgery to remove tumor tissue, the residual tissue still has a trend of growth and invasion, resulting in a high recurrence rate [45].

Therefore, it is crucial to exploit new drugs and modus for the treatment of gliomas.

It is well known that arsenic and its compounds are highly toxic, especially trivalent arsenic and pentavalent arsenic. Further studies have shown that ATO has an inhibitory effect on intractable diseases, including gliomas. The anti-cancer mechanisms of ATO include regulating apoptosis and autophagy, promoting the production of intracellular reactive oxygen species, and inhibiting tumor stem cells [46, 47]. Unfortunately, there are still many problems in ATO therapy, such as severe adverse reactions, high organ clearance, and poor blood–brain barrier permeability. Therefore, the design of drug carriers to overcome the BBB has become the focus of research. Tao et al. grafted polyacrylic acid (PAA) onto mesoporous silica nanoparticles (MSN) and combined them with angiopep-2-liposomes to prepare nanocarrier (ANG-LIP-PAA-MSN) (Fig. 5A) [48]. Figure 5B shows that modified agents are better absorbed by cells.

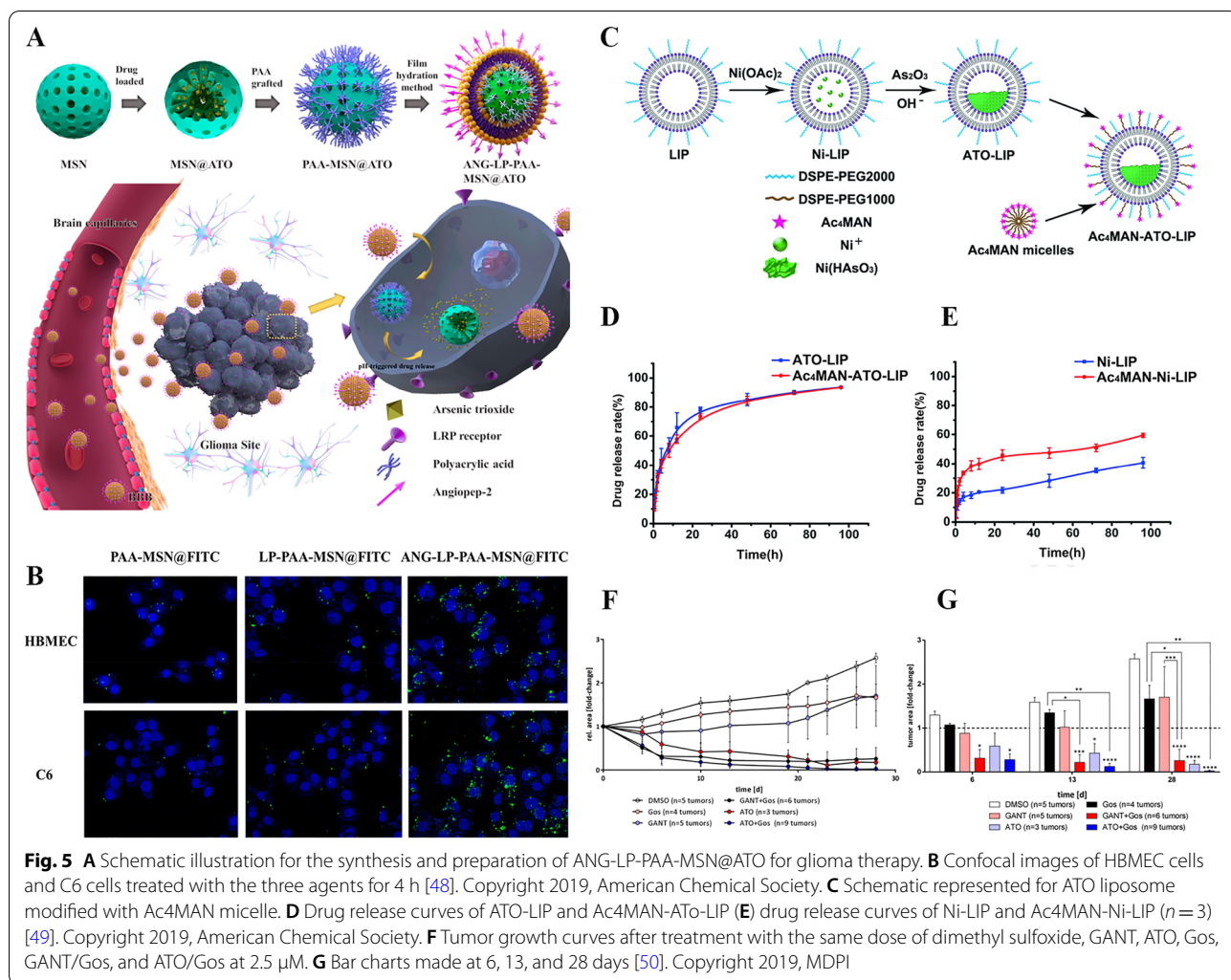


Fig. 5 **A** Schematic illustration for the synthesis and preparation of ANG-LP-PAA-MSN@ATO for glioma therapy. **B** Confocal images of HBMEC cells and C6 cells treated with the three agents for 4 h [48]. Copyright 2019, American Chemical Society. **C** Schematic represented for ATO liposome modified with Ac4MAN micelle. **D** Drug release curves of ATO-LIP and Ac4MAN-ATO-LIP (**E**) drug release curves of Ni-LIP and Ac4MAN-Ni-LIP ($n = 3$) [49]. Copyright 2019, American Chemical Society. **F** Tumor growth curves after treatment with the same dose of dimethyl sulfoxide, GANT, ATO, Gos, GANT/Gos, and ATO/Gos at 2.5 μM. **G** Bar charts made at 6, 13, and 28 days [50]. Copyright 2019, MDPI

Otherwise, Wang et al. showed that mannose (MAN) substrates without acetyl groups can promote the entry of vesicles into the brain, while the surface of LIP undergoes deacetylation of the Ac4MAN group under the action of enzymes, which is the “prodrug-like” characteristic of vesicles. Therefore, they insert distearoyl phospho-ethanolamine-polyethylene into the liposomes, thereby developing the “prodrug-like” ATO liposomes called Ac4MAN-ATO-LIP (Fig. 5C) [49]. Figure 5D, E show that liposomes modified with surfactants have a better drug release rate. To strongly suppress tumor growth or even tumor removal, Linder et al. designed a combination therapy consisting of the hedgehog signaling pathway inhibitors GANT61, anticancer drug gossypol (Gos), and ATO in Fig. 5F, G [50]. These provide a promising targeted therapy for the treatment of glioma.

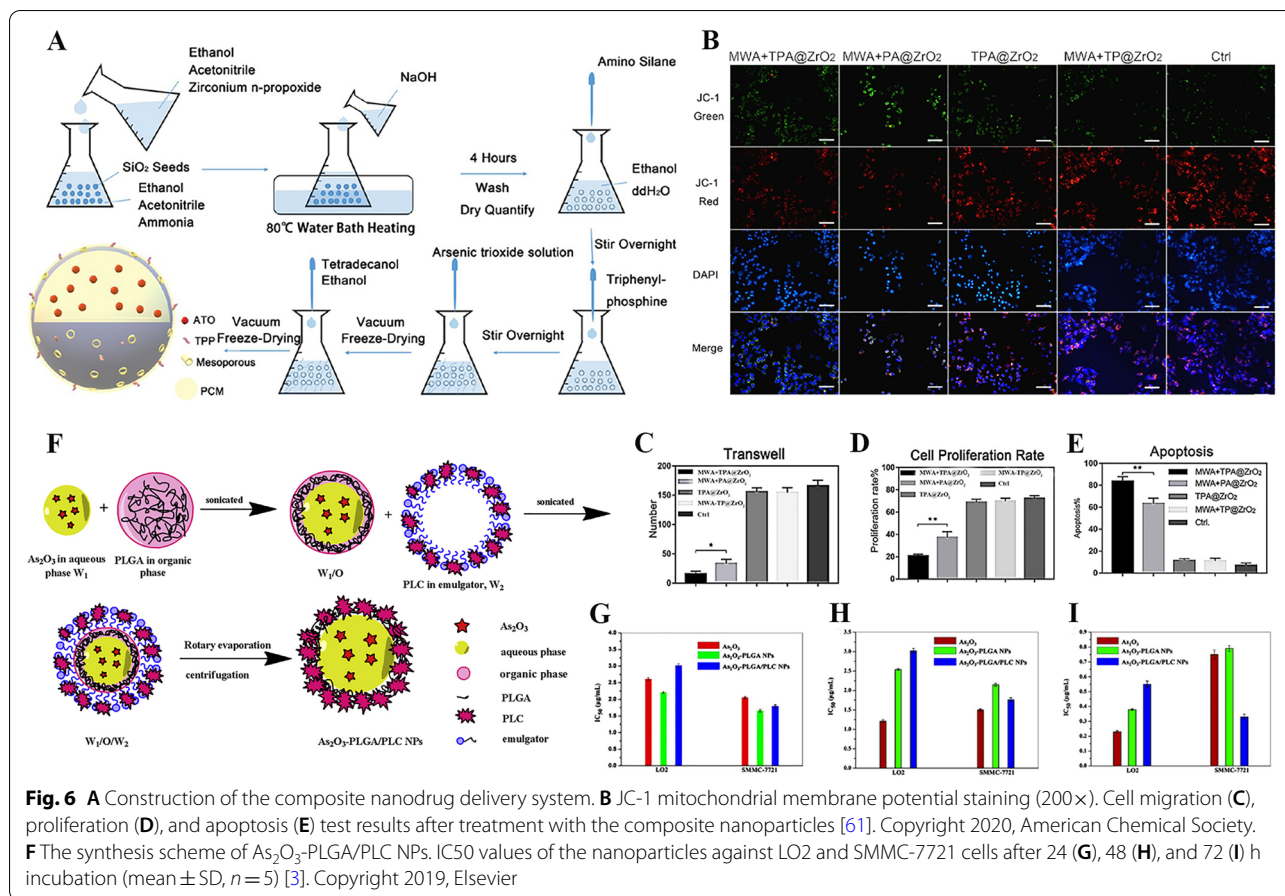
In addition, modifying groups on drug carriers can enhance the targeting ability by recognition and combination of the BBB, including angiopep-2 (ANG) and TGN peptides [48, 51, 52]. With the help of these groups, drugs are commendably accumulated in the tumor tissue area and play a role in targeted therapy. Other tumor-targeted modified peptides also ulteriorly enhance the penetration of the preparation, such as the internalizing RGD (iRGD, CRGDK/RGPD/EC) peptides. iRGD peptides can bind to the neuropilin-1 receptor of tumor cells, thus reducing cellular internalization. This suggests that we can design dual targeting nanomedicines to the blood–brain barrier and tumor. And using different nano-drug platform strategies according to different diseases is the trend of nanomedicine development in the future.

Hepatocellular carcinoma

The most popular pernicious tumor in the world is must belong to hepatocellular carcinoma, which is ranked the third one in cancer death. In the past decades, the hepatitis B virus (HBV) has been confirmed to be the main pathogenic factor. About 50–80% of liver cancer cases in the world are caused by HBV infection [53, 54]. Studies have shown that HBV infection can directly or indirectly lead to HCC through coinfection with hepatitis C virus, heavy drinking, or type 2 diabetes. The main mechanisms include HBV gene amalgamation, genomic uncertainty induced by variant, and activation of tumor signal pathway [55]. As the result of intense malignant and occultation of hepatocellular carcinoma, many patients with liver cancer have unsatisfactory surgical results, and the recurrence rate and mortality are high. Furthermore, HCC has high drug resistance in conventional chemotherapy and radiotherapy [56]. Therefore, it is a great challenge to develop therapeutic methods that can improve the efficacy and decrease the toxicity of HCC. ATO is a mineral drug with a positive curative effect on

a variety of tumors. It has the characteristics of multi-target and multi-efficacy of TCM and has been proved to have a positive effect on multifarious tumors. Nadra et al. studied the irradiation of normal liver and hepatoma cells (Hep3B) at 24, 48, and 72 h with different consistencies of ATO [57]. And the results show that ATO is promising to be a predominant drug for the curing of HCC.

However, on account of the systemic toxicity, swift renal elimination, and greater serum protein binding rate of ATO [58], ATO is seriously limited in the treatment of HCC [59]. We know that reducing the size of nanoparticles and preparing smaller ATO nanoparticles can improve the ability of nanoparticles to penetrate BBB and cell membranes. ATO microcrystalline microspheres with very high-density cores were prepared by embedding ATO microcrystalline with polylactide glycolic acid. ATO micro-crystal microspheres can continuously induce the production of reactive oxygen species and apoptosis of liver carcinoma cells. And reduce tumor growth by 80% through local administration. It realizes local management of ATO, avoids systemic exposure, and possesses higher pharmacological stress [60]. In recent years, chemotherapy combined with phototherapy and hyperthermia has obvious advantages in tumor treatment. Wu et al. developed a mitochondria-targeted carrier with local precisely controlled release of ATO by loading ATO into the cavities of nano zirconia microspheres [61]. After the ATO nano-drug was delivered to the tumor site through the enhanced permeability and retention effect, the tetradecyl alcohol was used as a phase change material (PCM) in vitro to be exposed to triphenylphosphine (TPP) by microwave control in vitro phosphine targets the ligand to enhance the mitochondrial killing effect of ATO. A kind of mitochondrial-targeted ATO controlled release carrier (TPP-PCM-ATO@ZrO₂) was constructed by coupling microwave-sensitive smart switches and mitochondrial targeting molecules outside the microspheres (Fig. 6A). The developed drug delivery system has (1) strong permeability and can inhibit tumor cell proliferation and promote apoptosis Fig. 6C–E, (2) controlled release of ATO in tumors, (3) ligands that can point mitochondria in Fig. 6B, (4) microwave therapy via an extracorporeal approach for improved efficacy. However, the mechanism of ATO mingled with microwave hyperthermia needs further study. Chitosan is a natural polysaccharide. Because of its good biocompatibility, biodegradability, and cytotoxicity to cancer cells, chitosan has become an ideal material for tumor treatment [62]. It is reported that by encapsulated ATO in PEG and lactic acid-modified chitosan (PLC). A nano-drug targeting ATO release from liver cancer cells was then prepared by coating with poly (lactide-co-glycolide) (PLGA) nanoparticles (As₂O₃-PLGA/PLC NPs)



(Fig. 6F). The prepared nano-drugs have good targeting to hepatocellular carcinoma and can effectively release ATO to cancer cells. Experimental studies showed that As_2O_3 PLGA/PLC NPs had an obvious inhibitory influence on human hepatoma cell lines SMMC-7721, but had low cytotoxicity on normal human hepatocytes (LO2 cells) in Fig. 6G–I [3]. Therefore, PLGA/PLC nanoparticles are a safe and effective drug carrier for liver cancer chemotherapy. Recent research reported the development of magnetic targeted nano-carrier technology has brought a new research direction for the effective transportation and release of ATO. Approach by modifying ATO prodrugs ($NiAsO_x$) loaded magnetic large-pore mesoporous silica nanoparticles (M-LPMSNs) with folic acid (FA), the responsiveness was prepared to released nano drugs (M-LPMSN- $NiAsO_x$ -FA). Further experiments show that the prepared nanomedicine has stronger cytotoxicity and the ability to promote cell apoptosis than the traditional free ATO [63]. ATO-containing magnetic silica nanoparticles can not only effectively resist hepatocellular carcinoma, but also have the ability to detect tumors in real-time. It has great application prospects and advantages in HCC treatment.

Cervical carcinoma

Cervical cancer is a common malignant tumor of the female reproductive system with a high incidence [64]. There are 500,000 new cases annually in the world. Comprehensive treatment including surgery is the main principle of treatment in the clinic. However, the cure rate of postoperative recurrence is less than 20%, in addition, chemotherapeutic drugs lack targeting and there are many side effects [65]. As there is no breakthrough in the comprehensive treatment of advanced cervical cancer, insights into the traditional mineral drug of ATO may be an alternative manner in cervical cancer treatment.

ATO has been proved to be effective in many cancers including cervical cancer. However, there is a lack of experiments to verify the anti-cervical cancer mechanism. Nowadays, Zhang et al. preliminary predict that ATO can induce reactive oxygen production to promote cell apoptosis by methyl thiazolyl tetrazolium (MTT) and flow cytometry. Western blotting and flow cytometry indicated that ATO suppresses hypoxia-inducible factor-1 α expression, which aimed to effectively inhibit the proliferation and invasion of Siha cells and promote apoptosis [65]. ATO due to the dose-limited toxicity

and poor pharmacokinetics in clinical trials requires the right vehicle to be carried [66]. The liposome is a common drug delivery carrier to encapsulate ATO in cervical cancer treatment. Liposomal ATO has been proved to exert better efficacy and lower cytotoxicity. At the same time, liposomes are regarded as a reservoir of drugs, and the slow release of drugs can avoid the toxic and side effects of high concentrations of ATO. Wang et al. showed that compared with free ATO, liposomal ATO further reduced the level of human papillomavirus-E6 protein and induced apoptosis of HeLa cells [67]. In addition, the concentration of arsenic in cells was measured by an inductively coupled plasma optical emission spectrometer (ICP-OES). Results showed that the intracellular concentration of ATO transported by liposomes was 3 times lower than that of free ATO, which verified the slow accumulation of ATO and lower cytotoxicity. The liposomes with different particle sizes and charges also have an impact on efficacy. Therefore, Akhtar utilized ICP-OES for the quantitative analysis of arsenic. Figure 7G, H show that neutral liposomes of 100 nm were

the highest drug loading rate, which was 24.2%As/P (± 0.848) [64]. In addition, the cytotoxicity test showed that neutral liposomes were the least toxic.

Other nano-preparations

The development of biomimetic nanoparticles and targeted drug delivery technology has opened up a new research path for mineral drugs. And the components of traditional Chinese medicine and mineral drugs are gradually attracting attention in the drug delivery system. For example, antigen and antibody recognition has high specificity and affinity, which is a very ideal targeted drug delivery carrier. CD44v6 is a membrane antigen overexpressed in epithelial tumors such as pancreatic cancer, hepatocellular carcinoma, and breast cancer. The anti-CD44v6 single-chain variable fragment (scFv (CD44v6)) screened from the human phage antibody library was assembled into vesicles with an amphiphilic copolymer. Arsenite ions (As) were encapsulated in the core of vesicles to prepare vesicle nanoparticles (scFv-As-NPs). Experiments showed that the prepared

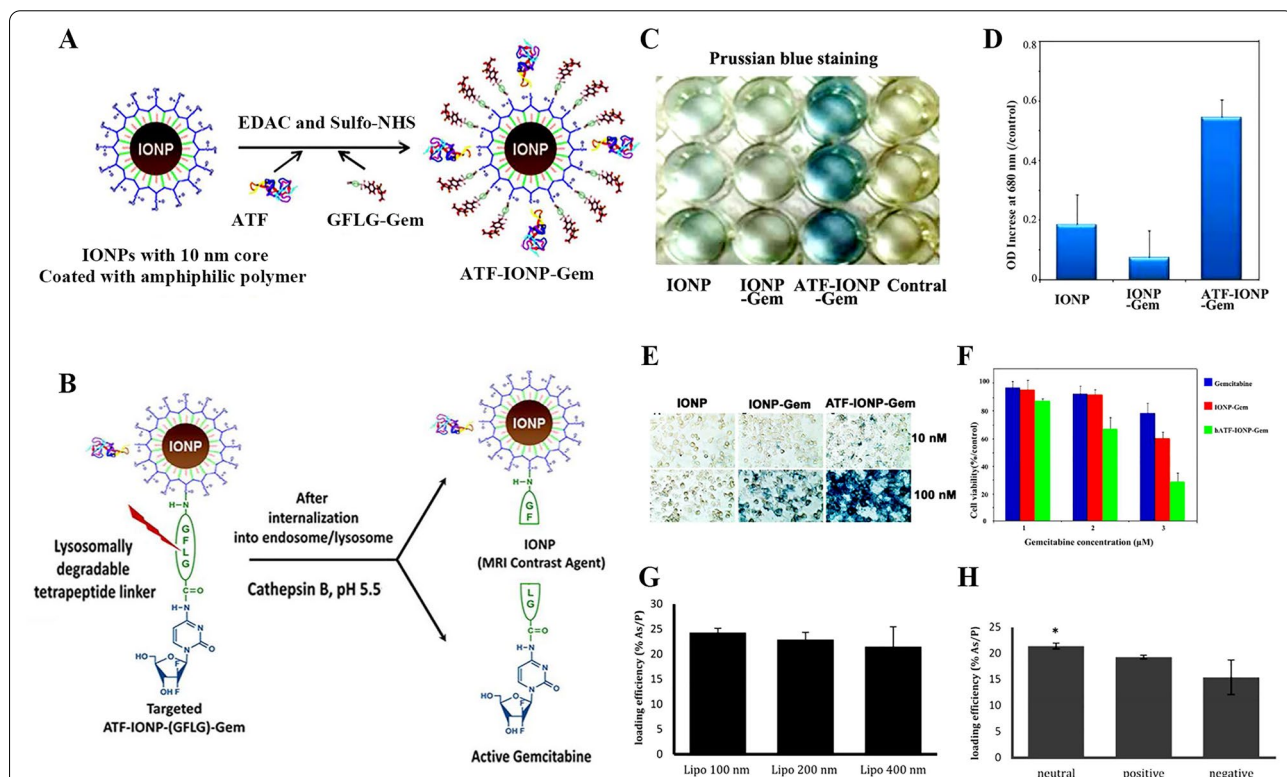


Fig. 7 A Schematic of the preparation of ATF-IONP-Gem. B Drug release condition and efficiency. IONPs, IONP-Gem, ATF-IONP-Gem, and human pancreatic cancer cells were incubated in 100 nm and 10 nm for 4 h, then Prussian blue staining was performed. C IONPs in cells were detected as blue-stained cells. D the OD value was quantitatively detected at 680 nm with a micro board reader. E The observed bright-field microscopic images of Prussian blue-stained cells under 40 × magnifications. F the number of living cells per well in a 96-well tissue culture plate was determined by the MTT method [76]. Copyright 2013, American Chemical Society. G The drug loading rate of synthetic liposomes was determined by inductively coupled plasma optical emission spectrometry (ICP-OES) at different particle sizes and (H) different charges [64]. Copyright 2019, MDPI

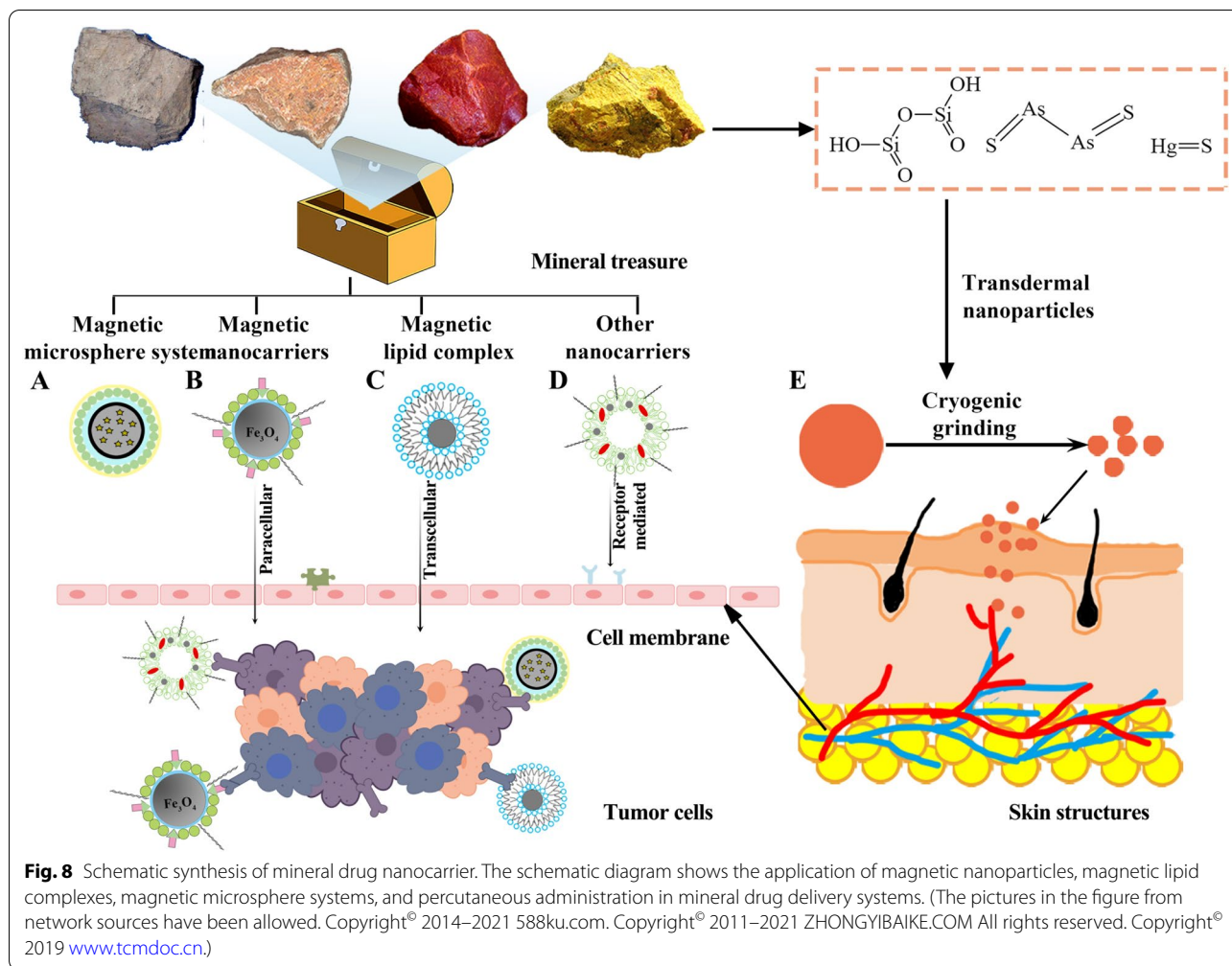


Fig. 8 Schematic synthesis of mineral drug nanocarrier. The schematic diagram shows the application of magnetic nanoparticles, magnetic lipid complexes, magnetic microspheres systems, and percutaneous administration in mineral drug delivery systems. (The pictures in the figure from network sources have been allowed. Copyright© 2014–2021 588ku.com. Copyright© 2011–2021 ZHONGYIBAIKE.COM All rights reserved. Copyright© 2019 www.tcmdoc.cn.)

arsenic nanovesicles had a better effect of inhibiting tumor growth and promoting tumor cell apoptosis, providing an efficient and safe platform for the delivery of mineral drug arsenic [68]. (–)-Epigallocatechin-3-gallate (EGCG) is a phenolic compound with rich content of tea polyphenols and good anti-tumor activity. Recent studies have shown that the combination of EGCG and metal ions can significantly improve drug activity and reduce metal toxicity, more importantly, it is also a good nano-drug carrier [69, 70]. Wei et al. combined the realgar with EGCG and prepared the nano-drug (EGCG-RNPs) by coprecipitation method. It was proved that EGCG as a carrier could significantly increase the uptake of HL-60 cells to realgar, which provided a new treatment for APL. In recent years, the great advantage of protein biomineralization to synthesize nanoparticles to enhance the synergistic effect of drugs has been reported in the literature. Macrophage membrane has good biocompatibility and can be used as a carrier for biomimetic nano preparations. During the treatment of atherosclerosis, Huang

et al. [71] used macrophage membranes to wrap Fe_3O_4 to prepare liposome $\text{Fe}_3\text{O}_4\text{@M}$ nano-drugs, which can be used for magnetic resonance targeted detection, which can better detect and treat the early stage of the disease stage. Bovine serum protein is also a common biomimetic nanomaterial. FeS_2 nanoparticles synthesized by protein biomineralization have synergistic tumor therapeutic effects in vivo and in vitro photothermal photodynamic therapy and have no significant toxicity [72]. All these have proved that compared with traditional preparations (pills, powders, decoctions, etc.), modern pharmaceutical preparations can give full play to the characteristics of low-dose, low-toxicity, targeted transportation, and better play the role of mineral medicine effect.

Carrier function of mineral medicine in disease diagnosis and treatment

Magnetic nanoparticles

With the growing trend of drug delivery system research, nanotechnology has become the focus of

modern research owing to its target ability, longer circulation in vivo, and fewer side effects [73]. Among them, magnetic nanoparticles have many effects in cancer treatment for their good biocompatibility, quick magnetic response, and excellent fluorescence imaging. And it exhibits good application prospects in magnetic resonance imaging (MRI), magnetic fluid hyperthermia (MFH), and magnetic drug targeting (MDT) therapy. MRI is based on the fact that magnetic nanoparticles are coupled with fluorescent agents for clinical optical diagnosis. The report has shown that tumors can form damage or deactivation when the temperature reaches or exceeds 43 °C. Therefore, the principle of MFH is to apply high temperatures to kill cancer cells [74]. As shown in Fig. 8B, magnetic nanoparticles (MNPs) can utilize a magnetic field to generate heat to achieve the purpose of thermotherapy for their excellent magnetism. However, it may also cause damage to normal and healthy cells probably owing to the lack of selectivity of hyperthermia. Drug targeting is the key to specific therapy, and magnetic nanoparticles can effectively accumulate in the target tissue and site when magnetic fields take effect. In addition, MNPs can also exert active targeting through selective through its targeting ligands binding to tumor over-expressed receptors [75]. When MRI, MFH, and MDT combine, showing effective diagnosis and treatment.

The general preparation methods of MNPs include coprecipitation and organic thermal decomposition. The coprecipitation method is prone to nano-agglomeration. Therefore, the precipitation hydrolytic alkali method, has relatively good stability and dispersion without high boiling point solvent and high temperature, suggesting a good substitute [76]. In magnetic nanoparticles, drugs can be coupled through covalent or non-covalent pathways. Non-covalent coupling refers to physical adsorption and entrapment, while covalent binding refers to the formation of covalent chemical bonds between MNPs and drug molecules. Covalent binding between drug loading and release is more difficult than non-covalent binding. Moreover, the residual catalyst in the binding process is also toxic to the physiological environment. When MNPs reach the designated site, it is released under-stimulation, including chemical and biochemical stimuli and external magnetic, light, and thermal stimuli.

Nanoparticles have always shown excellent efficacy in the treatment of cancer. However, there are some problems to be further studied, such as less targeted accumulation in vivo, short cycle time, ease to be eviscerated, and so on. Therefore, optimizing the physicochemical properties and modifying the surface of nanoparticles has become the focus of follow-up research [77]. The report showed that the target ligand, an amino-terminal

fragment (ATF) peptide, binds to the urokinase plasminogen activator receptor. Targeted delivery of the hydrophilic drug gemcitabine (Gem) by coupling with magnetic iron oxide nanoparticles (IONPs) (Fig. 7A, B). Figure 7C, D showed that cell uptake was significantly increased in the ATF-IONP-Gem group after Prussian blue staining, about three times as much as in the non-targeted group. Figure 7E shows that in the IONPs-Gem group without ATF modification, the cell uptake of cancer cells was still quite low even at high concentrations, indicating that the modification of ATF enhanced the targeted therapy of drugs. In addition, Fig. 7F shows that the cytotoxicity experiment showed that the ATF-IONP-Gem group had a better level of cell survival than other groups, demonstrating that it reduced the cytotoxicity [78]. Folic acid-modified magnetic iron oxide bovine serum albumin (BSA) nanoparticles were also designed. At the same time, doxorubicin (DOX) was loaded to achieve the purpose of targeted therapy, and the key to targeted therapy was folate receptor overexpression cells in tumors [79]. Through the observation of transplanted tumor tissue sections, the results showed that the FA-DOX-BSA MNP hyperthermia group showed significant differences from MFH and MDT groups in an inflammatory response and cell necrosis. This indicates that targeting ligand coupling magnetic nanoparticles possess good antineoplastic activity. In addition, Lee et al. utilized silica magnetic nanoparticles to load drugs. Silica-mediated nanoparticles have stable chemical properties, low cytotoxicity, and large pore volume, which can provide a better platform to carry drugs and imaging agents [80].

Magnetic lipid complex

As an endogenous nano-carrier, liposome is composed of three major biological components: phospholipid bilayer, transmembrane proteins, and internal core. Liposomes have the following advantages: (1) high biocompatibility and low toxicity, (2) the ability to carry both water-soluble and water-insoluble drugs, (3) the highly modifiable surface, (4) the controllable size. MNPs exert multi-mode therapy in clinical treatment and become the focus of modern diagnosis and treatment [2]. Liposome and magnetic nanoparticles are utilized to be shell and core, respectively. This core-shell structure, also known as lipid magnetic nanoparticles (MLs), can effectively maintain the colloid stability of nanoparticles and prevent drug leakage (Fig. 8C). In the bilayer membrane of liposomes, the inner membrane is firmly adsorbed on the magnetic nanocomposites. While the outer membrane is relatively loose and easy to functionalize. For example, polyethylene glycol is utilized to perpetuate the cycling time in vivo. Otherwise, the modification of targeted ligands and fluorescent agents is to achieve drug

targeting and bimodal imaging, respectively. Choi et al. reported that magnetic liposomes showed a strong anti-cancer effect and tumor targeting on colorectal cancer cells of CT26 mice under the action of an external magnetic field [81]. Ketkar et al. achieved high hepatocyte targeting by designing lactose functionalized magnetic liposomes [82]. Soenen et al. reported that MLs can perform simultaneous MRI and fluorescence imaging because of the particularity of the bilayer of liposomes [83, 84]. Therefore, the organic combination of liposomes and magnetic nanoparticles is the optimization of a single delivery carrier among them. In addition, the research began to pay attention to some new types of liposomes, which not only have the advantages of liposomes but also have their unique properties. For example, pH-sensitive liposomes can be selectively released in weakly acidic tumor anaerobic areas [85].

Magnetic microsphere system

Microsphere refers to the dispersion system formed by drug dispersion in natural polymers and matrix polymers. Natural polymers comprise starch, albumin, and gel [86]. The matrix polymers of microspheres include polylactic acid, polylactic acid glycolic acid, and chitosan. Among them, PLGA has become the first choice of drug carriers for its high stability and entrapment efficiency [87]. Therefore, the microspheres show good biocompatibility, biodegradability, and sustained release. However, the clinical study indicates that restrictions of microsphere preparation have remained, such as low drug loading, low targeting, and poor stability [88].

Now, most studies have focused on strategies to improve drug loading and release. These strategies can be divided into four groups: (1) optimization of polymers: low molecular weight and hydrophobicity, (2) regulation of the external water phase pH, (3) increased polymer concentration, (4) emulsifier addition. Otherwise, Fig. 8A illustrates the application of magnetic nanoparticles (MNPs) to encapsulated microspheres is also gradually emerging. MNPs have excellent magnetic targeting and colloidal stability. Thus, the combination of magnetic nanoparticles and microspheres can play their respective advantages. And that provides a new direction for the clinical treatment of nanometer micro balloons. Srinivasan Ayyanaar and other researchers designed an associated system composed of iron oxide nanoparticles and poly (D,L-lactide-co-glycolic acid) to load curcumin [89]. MTT and cell colony formation experiments showed that the designed nano-system exhibited satisfactory cytotoxicity to cancer cells and could effectively inhibit cell colony-forming. Moreover, the morphological characterization experiments showed that the system also had good stability. In addition, the drug liberates tentative

showed that the drug was targeted released in cancer cells under the action of the magnetic field. These experimental results show that the microspheres encapsulated by magnetic nanoparticles can better solve the problem of single microsphere preparation.

Other nanocarriers

Except for microspheres and liposomes, Fe_3O_4 NPs can also be designed as other preparations, including gels, vaccines, and aerosols. Nahid and other researchers designed multi-stimulus-responsive magnetic nanohydrogels (MNHGs) to load doxorubicin hydrochloride [90]. The results of anti-cervical cancer experiments demonstrated that compared with single magnetic nanoparticles, MNHGs showed higher drug loading rate and cytotoxicity. In addition, owing to their superior pH, magnetic field, and thermal response, MNHGs show splendid targeting ability. Yi Zhao et al. focused on the potential of iron oxide nanoparticles to be adjuvants for cancer vaccines. In this research Fe_3O_4 NPs not only work as an antigen presentation system but also as immune enhancers for antigens. The results of immune response and anti-colon tumor experiments showed that the preparation induced a stronger immune response and improved the anti-tumor effect [91, 92]. Of note, Fe_3O_4 NPs owing to their superior magnetic targeting provide a new idea for the aerosol treatment of bronchogenic carcinoma. Mehdi Mohammadi et al. verified the targeted therapeutic effect of magnetic aerosol drug targeting through the Weibel symmetrical tree lung model [93].

Halloysite is a submicron hollow cylindrical aluminosilicate clay. Halloysite is a natural carrier with good biocompatibility and sustained-release properties, which can be used to transport a variety of drugs (Fig. 8D) [94–97]. Viviana et al. designed halloysite nanotubes to transport resveratrol. The system has shown an ideal encapsulation effect and an excellent ability to release the drug slowly, thus improving the efficacy of tumor therapy [98]. A novel co-delivery method of polysulfone mucopolysaccharides embedded in amine-functionalized halloysite nanotubes is reported in this paper. For this reason halloysite nanotubes are ideal materials with large pores that can absorb the mucus barrier and are sensitive to pH value. In addition, the delivery system can improve the stability of lactase and enhance the permeability of drug-entrapped mucosa [99]. This new microcapsule design provides a promising solution for the development of oral formulations.

Discussion on transdermal drug delivery

Transdermal drug delivery is a kind of drug delivery modus, which makes the drug enter the blood circulation through the skin and mucous membrane. The way of

treating diseases by skin medication has a long history of application in TCM preparation. For example, the medicinal paste in TCM is a representative and early transdermal delivery system. Its unique pattern of administration determines that transdermal drug delivery has the following characteristics: (1) The first-pass effect of the liver is avoided. (2) The degradation of drugs in the gastrointestinal tract was avoided. (3) It can not only play a role of systemic therapy but also act the part of local therapy. (4) It can make the drug hold a constant blood density, and reduce the number of drug administration. (5) The method of skin administration is safe and convenient. In the literature related, partial transdermal administration is favorable for the treatment of highly localized nubbles, such as breast cancer and cervical carcinoma [99–103]. However, the efficacy of percutaneous administration is often affected by the stability of microorganisms or enzymes on the skin surface and drug particles. This prompted researchers to seek new transdermal drug technology. For example, combined nanoparticles, liposomes, microspheres and another nano-sized particles with transdermal technology to design novel transdermal formulations can greatly improve the therapeutic effect. Toyoda et al. effectively delivered the nanogel containing antigen peptide to tumor cells through the skin by the cancer antigen inoculation test, which proved that the method of delivery antigen peptide via the skin is very beneficial to inhibit the growth of tumor [104]. The application of fresh techniques and methods provides a new research path for the transdermal drug delivery system. For example, realgar has been largely used since ancient times in the curing of various diseases, including snakebite, convulsions, and malaria. Modern research has also certificated that realgar has great potential in the treatment of various hematologic and solid tumors, such as breast cancer, granulocytic leukemia, skin cancer, etc. [105, 106]. Similarly, water-insolubility and toxicity have always been difficult problems limiting the clinical application of realgar. Here, Qi and his team used a transdermal delivery system for the first time to deliver realgar nanoparticles and evaluated their anticancer effects and toxicity in vivo (Fig. 8E). The result indicated that compared with intraperitoneal administration, transdermal delivery of realgar nanoparticles could significantly dwindle tumor volume, with higher efficacy and lower systemic toxicity [107]. At present, there are few studies on the transdermal delivery of mineral drugs. Traditional ointments involving mineral drugs have unique therapeutic advantages and long application history. However, there are still many problems to be solved in mineral drug transdermal preparations. The mechanisms of action of most mineral drugs and their interactions with diseases, the toxicity of mineral drugs, and the accumulation of

heavy metals after transdermal administration are still unclear and need to be studied. Therefore, percutaneous administration of mineral drugs is a promising and challenging direction.

Conclusions

Mineral medicines, as an integral part of the traditional medicinal culture, have been playing an important role for more than two millennia. Only 32.9% of mineral drug resources have been documented in the 2020 edition of the Chinese Pharmacopoeia [108], while mineral resources are widespread and have unique curative effects. Therefore, the development, research, and application of mineral drugs are still promising.

Mineral medicine, same as animal medicine and botanical drug, is an indispensable part of TCM. Mineral medicines have a lengthy history of application and reliable clinical efficacy. Experts in TCM of the past generations have summed up many valuable medicines' experiences and theories. Along with the advance of modern scientific knowledge, mineral medicines have also shown significant advantages in multiple malignant tumors therapy [23]. Mineral drugs commonly include heat-clearing mineral drugs (gypsum, mirabilite, realgar, etc.), hemostatic mineral drugs (ochre, alum, forged gypsum, etc.), sedative mineral drugs (cinnabar, lapis lazuli, magnetite), and insecticidal mineral drugs (cinnabar, calamine, etc.). For example, "Angong Niu Huang Pill" is an outstanding Chinese patent medicine, which mainly contains two mineral medicines of cinnabar (HgS) and realgar (As₄S₄). It has been popularly used for thousands of years to cure the central nervous process and cardiovascular diseases. Modern clinical treatment for brain trauma, hemorrhage, and coma has an excellent effect [109–113]. In addition, the coronavirus pneumonia disease that broke out in 2020 is raging all over the world, threatening the life of all mankind. Surprisingly, "Lianhua Qingwen capsule" and "Qingfei paidu decoction" have achieved very positive results in anti-novel coronavirus and life-saving. And these are well-known traditional Chinese medicine prescription preparations. In the above two kinds of TCM, there is an important mineral drug: gypsum. Gypsum is outstanding for its efficacy in clearing heat-fire and promoting fluid production. And doctors of TCM have commonly applied gypsum in exogenous fever, lung heat, asthma, cough, and other diseases. Therefore, it has broad prospects for an inheritance, especially in the exploration and forthputting of mineral drugs.

However, similar to the problems encountered in the study of all TCM components, the extensive pharmacological activity and clinical efficacy of mineral medicines are still to be studied. Besides, the pharmacological mechanism still needs a lot of exploration. In addition,

the safety of mineral drugs is still the bottleneck in their development as a result that most mineral drugs contain a large number of heavy metals. For example, cinnabar is often used to treat neurological diseases [114–116]. And reports indicate that cinnabar and its main component HgS have low cytotoxicity. In *in vitro* experiments, the survival rate of cells in the environment of large-dose cinnabar and HgS is about 65%, higher than HgCl₂ and MeHg. That means cinnabar has no significant effect on the intracellular mercury content [117]. However, studies have pointed out that even therapeutic doses of cinnabar have potential neurotoxicity [118]. Studies have pointed out that the cure and venom dosage of cinnabar have distinct pathways and targets in the cerebral cortex [114]. Moreover, the latent molecular mechanism of the pharmacodynamics and toxicological activities of cinnabar is still being explored. Some traditional mineral medicines in TCM are not used as medicines to play a therapeutic role in modern applications. Such as magnetite as a contrast agent component in the imaging of early atherosclerotic lesions [119]. This provides us with a very promising idea for the development of new pharmaceutical excipients, which embodies the advantages of the combination of TCM and accessories. Although there are some limitations in the methods of studying the pharmacological action and mechanism of a single mineral component. Considering that the mineral component is small and relatively simple, this research idea can also provide some references for the further study of mineral drugs [119].

At present, many works of literature have given an account of the therapeutic effects of the mineral drugs in a variety of malignant tumors, such as in the therapeutics of promyelocytic leukemia, gastric cancer, etc [120–124]. However, the safety issues such as heavy metals and hazardous elements in mineral drugs still limit the clinical use of mineral drugs. For example, the existing mineral preparations such as Daqi Li powder, Jiuhua ointment, and Half-sulfur pills on the market have shown therapeutic effects in removing blood stasis and swelling, repairing skin wounds. However, even at the dosage used, mineral medicines still unavoidably have certain hepatotoxicity and nephrotoxicity, as well as the accumulation of heavy metals. Therefore, it is very necessary for the development and utilization of mineral medicines to optimize mineral medicine preparations, improve the curative effects, and reduce toxicity by taking advantage of modern preparations.

New drug delivery systems and formulation technologies have established strategies for the study of mineral drugs in TCM, enabling many breakthroughs in the development and utilization of mineral drugs. The application of nanocarriers and biomaterials provides feasible opportunities for the construction of mineral drug

nano-delivery platforms. Liposomes, exosomes, and polymer nanoparticles are widely used in nano-medicine for their superior biocompatibility. And they can be effectively designed as carrier materials for transporting mineral nanoparticles. It provides more possibilities for mineral drugs to play a therapeutic role. And they can be effectively designed as carrier materials for transporting mineral nanoparticles. It provides more possibilities for mineral drugs to play a therapeutic role. On the other hand, the unique properties and structures of mineral drugs have also shown great latent in the study of drug delivery carriers. Such as silicon dioxide coating which can protect insulin-loaded liposomes from degradation by digestive enzymes [16]. And another, calcium sulfate supports vancomycin nano-systems, which can significantly enhance their antibacterial properties [125].

So far, more studies on arsenic and iron preparations have been reported. The establishment of novel drug delivery systems greatly improves the drug loading and targeting of ATO, while the research on iron is mainly in MRI imaging ability and carrier research. Recently, many pharmacological activities of magnetic targeting systems have shown significant advantages, and iron minerals such as iron oxide have been further studied as drugs and carriers. In addition, in the design of mineral medicine preparations, due to the reduction in the amount of mineral medicine used, it is also possible to choose another medicine to match it. Under the synergistic treatment, it can better exert the efficacy of mineral medicine itself and reduce the dose toxicity, which is not only safer to use, but also effective even better.

In this review, we systematically describe the chemical constituents, pharmacological actions, and applications in delivery systems of mineral drugs of Chinese medicine, such as preparing multifunctional nanoparticles to deliver ATO to heighten the treatment of HCC. Despite the significant achievements in the research of mineral medicines delivery systems, there are still exist some challenges. The toxicity and safety of mineral drugs are still the focus of attention, and the more efficient and safe delivery matrix needs to be excavated. In addition, this review focuses on the research achievements of TCM mineral drugs in transport systems, including the curing of malignant burls and the progress in delivery vehicles. It is expected to overcome the defects of poor solubility, low bioavailability, and strong toxicity of TCM. Hopefully, under the reference of this article, it can help to tap more potential of mineral drugs in the research of drug delivery systems. Whether as medicaments or nano-delivery vehicles, we are all willing and eager to witness that.

Abbreviations

AML: Acute myeloid leukemia; ANG: Angiopep-2; APL: Acute promyelocytic leukemia; ATF: Amino-terminal fragment; ATO: Arsenic trioxide; ATRA: All-trans retinoic acid; BBB: Blood-brain barrier; BHD: Bai-Hu decoction; BSA: Bovine serum albumin; BSM: Basilicum seed mucilage; CPX: Cephalexin; DCQD: Dachengqi decoction; DOX: Doxorubicin; EGCG: (−)-Epigallocatechin-3-gallate; FA: Folic acid; Gem: Gemcitabine; Gos: Gossypol; HBMEC: Human brain microvascular endothelial cells; HBV: Hepatitis B virus; HCC: Hepatocellular carcinoma; ICP-OES: Inductively coupled plasma optical emission spectrometry; IL-17: Interleukin-17; IL-1β: Interleukin-1β; IONPs: Iron oxide nanoparticles; iRGD: Internalizing RGD; LIP: Liposomes; LO2: Normal human hepatocytes; MAN: Mannose; MDT: Magnetic drug targeting; MFH: Magnetic fluid hyperthermia; MLs: Magnetoliposomes; M-LPMSN: Magnetic large-pore mesoporous silica nanoparticles; MNHGs: Magnetic nano-hydrogels; MNPs: Magnetic nanoparticles; MRI: Magnetic resonance imaging; MSN: Mesoporous silica nanoparticles; MTT: Methyl thiazolyl tetrazolium; NPs: Nanoparticles; PAA: Polyacrylic acid; PCM: Phase change material; PEG: Polyethylene glycol; PLC: Polyethylene glycol and lactobionic acid modified chitosan; PLGA: Poly(lactide-co-glycolide) acid; RA: Retinoic acid; RNPs: Realgar nanoparticles; scFv: Single chain variable fragment; TCM: Traditional Chinese medicine; TNF-α: Tumor necrosis factor-α; TNF: Tumor necrosis factor; TPP: Triphenylphosphine.

Acknowledgements

Not applicable.

Authors' contributions

XZ: Investigation, Software, Writing—original draft. ZD: Software, Validation, Writing—original draft. YX: Software, Validation, QL: Writing—original draft, KF: Writing—original draft, YZ: Writing—review and editing, LD: Conceptualization, Resources, Writing—review and editing, Project administration. RW: Conceptualization, Supervision, Resources, Writing—review and editing, Project administration. All authors read and approved the final manuscript.

Funding

This article is supported by the National Natural Science Foundation of China (No. 81903557, 82074024), Natural Science Foundation of Jiangsu Province (No. BK20190802), Natural Science Foundation Youth Project of Nanjing University of Chinese Medicine (No. NZY81903557), the Open Project of Chinese Materia Medica First-Class Discipline of Nanjing University of Chinese Medicine (No. 2020YLXK019), and College Students' Innovative Entrepreneurial Training of Nanjing University of Chinese Medicine (No. 202110315097Z and 202110315021).

Availability of data and materials

Not applicable.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

Author details

¹College of Pharmacy, Nanjing University of Chinese Medicine, Nanjing 210023, China. ²Jiangsu Provincial TCM Engineering Technology Research Center of High Efficient Drug Delivery System, Nanjing 210023, China.

Received: 7 November 2021 Accepted: 28 January 2022

Published online: 10 February 2022

References

- Ettlinger R, Moreno N, Volkmer D, Kerl K, Bunzen H. Zeolitic imidazolate framework-8 as pH-sensitive nanocarrier for "Arsenic Trioxide" drug delivery. *Chemistry*. 2019;25(57):13189–96. <https://doi.org/10.1002/chem.201902599> (Epub 2019 Sep 13).
- Jin Z, Yi X, Yang J, Zhou M, Wu P, Yan G. Liposome-coated arsenic-manganese complex for magnetic resonance imaging-guided synergistic therapy against carcinoma. *Int J Nanomed*. 2021;1(16):3775–88. <https://doi.org/10.2147/IJN.S313962>.
- Song X, Wang J, Xu Y, Shao H, Gu J. Surface-modified PLGA nanoparticles with PEG/LA-chitosan for targeted delivery of arsenic trioxide for liver cancer treatment: inhibition effects enhanced and side effects reduced. *Colloids Surf B Biointerfaces*. 2019;1(180):110–7. <https://doi.org/10.1016/j.colsurfb.2019.04.036> (Epub 2019 Apr 16).
- Song P, Hai Y, Wang X, Zhao L, Chen B, Cui P, Xie Q, Yu L, Li Y, Wu Z, Li H. Realgar transforming solution suppresses angiogenesis and tumor growth by inhibiting VEGF receptor 2 signaling in vein endothelial cells. *Arch Pharm Res*. 2018;41(4):467–80. <https://doi.org/10.1007/s12272-018-014-6> (Epub 2018 Mar 15).
- Rayegan A, Allafchian A, Abdolhosseini Sarsari I, Kameli P. Synthesis and characterization of basil seed mucilage coated Fe₃O₄ magnetic nanoparticles as a drug carrier for the controlled delivery of cephalexin. *Int J Biol Macromol*. 2018;1(113):317–28. <https://doi.org/10.1016/j.ijbmac.2018.02.134> (Epub 2018 Feb 23).
- Liu R, Li X, Huang N, Fan M, Sun R. Toxicity of traditional Chinese medicine herbal and mineral products. *Adv Pharmacol*. 2020;87:301–46. <https://doi.org/10.1016/bs.apha.2019.08.001> (Epub 2019 Oct 18).
- Khalifehazadeh R, Arami H. Biodegradable calcium phosphate nanoparticles for cancer therapy. *Adv Colloid Interface Sci*. 2020;279:102157. <https://doi.org/10.1016/j.cis.2020.102157> (Epub 2020 Apr 10).
- Palanisamy S, Wang YM. Superparamagnetic iron oxide nanoparticulate system: synthesis, targeting, drug delivery and therapy in cancer. *Dalton Trans*. 2019;48(26):9490–515. <https://doi.org/10.1039/c9dt00459a>.
- Das M, Solanki A, Joshi A, Devkar R, Seshadri S, Thakore S. β-cyclodextrin based dual-responsive multifunctional nanotheranostics for cancer cell targeting and dual drug delivery. *Carbohydr Polym*. 2019;15(206):694–705. <https://doi.org/10.1016/j.carbpol.2018.11.049> (Epub 2018 Nov 20).
- Rafiee F, Haghi F, Bikas R, Heidari A, Gholami M, Kozakiewicz A, Zeighami H. Synthesis, characterization and assessment of anti-quorum sensing activity of copper(II)-ciprofloxacin complex against *Pseudomonas aeruginosa* PAO1. *AMB Express*. 2020;10(1):82. <https://doi.org/10.1186/s13568-020-01017-3>.
- Yin M, Lin X, Ren T, Li Z, Ren X, Huang TS. Cytocompatible quaternized carboxymethyl chitosan/poly(vinyl alcohol) blend film loaded copper for antibacterial application. *Int J Biol Macromol*. 2018;120(Pt A):992–8. <https://doi.org/10.1016/j.ijbiomac.2018.08.105> (Epub 2018 Aug 31).
- Hildebrand S, Löwa N, Paysen H, Fratila RM, Reverte-Salisa L, Trakoolwilaiwan T, Niu Z, Kasparis G, Preuss SF, Kosch O, de la Fuente MJ, Thanh NTK, Wiekhorst F, Pfeifer A. Quantification of lipoprotein uptake in vivo using magnetic particle imaging and spectroscopy. *ACS Nano*. 2021;15(1):434–46. <https://doi.org/10.1021/acsnano.0c03229> (Epub 2020 Dec 11).
- Zhou J, Hou J, Liu Y, Rao J. Targeted delivery of β-glucosidase-loaded magnetic nanoparticles: effect of external magnetic field duration and intensity. *Nanomedicine (Lond)*. 2020;15(21):2029–40. <https://doi.org/10.2217/nmm-2020-0186> (Epub 2020 Sep 4).
- Wahajuddin AS. Superparamagnetic iron oxide nanoparticles: magnetic nanopatforms as drug carriers. *Int J Nanomed*. 2012;7:3445–71. <https://doi.org/10.2147/IJN.S30320>.
- Xu JK, Zhang FF, Sun JJ, Sheng J, Wang F, Sun M. Bio and nanomaterials based on Fe₃O₄. *Molecules*. 2014;19(12):21506–28. <https://doi.org/10.3390/molecules191221506>.
- Mohanraj VJ, Barnes TJ, Prestidge CA. Silica nanoparticle coated liposomes: a new type of hybrid nanocapsule for proteins. *Int J Pharm*. 2010;392(1–2):285–93. <https://doi.org/10.1016/j.ijpharm.2010.03.061> (Epub 2010 Apr 2).
- Ingle SG, Pai RV, Monpara JD, Vavia PR. Liposils: an effective strategy for stabilizing Paclitaxel loaded liposomes by surface coating with silica. *Eur J Pharm Sci*. 2018;15(122):51–63. <https://doi.org/10.1016/j.ejps.2018.06.025> (Epub 2018 Jun 21).
- Amin MU, Ali S, Ali MY, Tariq I, Nasrullah U, Pinnapreddy SR, Wölk C, Bakowsky U, Brübler J. Enhanced efficacy and drug delivery with lipid coated mesoporous silica nanoparticles in cancer therapy. *Eur J Pharm*

- Biopharm. 2021;165:31–40. <https://doi.org/10.1016/j.ejpb.2021.04.020> (Epub 2021 May 4).
19. Meng H, Wang M, Liu H, Liu X, Situ A, Wu B, Ji Z, Chang CH, Nel AE. Use of a lipid-coated mesoporous silica nanoparticle platform for synergistic gemcitabine and paclitaxel delivery to human pancreatic cancer in mice. *ACS Nano*. 2015;9(4):3540–57. <https://doi.org/10.1021/acs.nano.5b00510> (Epub 2015 Mar 31. Erratum in: *ACS Nano*. 2016 Jun 28;10(6):6416).
 20. Lü P, Li X, Chen JW. Study on the speciation of calcium in Baihu decoction. *Guang Pu Xue Yu Guang Pu Fen Xi*. 2010;30(10):2824–6 (Chinese).
 21. Jia LL, Li R, Ma J, Fan Y, Li HB. Effects of Bai-Hu decoction on fever induced by lipopolysaccharide. *Kaohsiung J Med Sci*. 2013;29(3):128–32. <https://doi.org/10.1016/j.kjms.2012.08.022> (Epub 2013 Jan 31).
 22. Xiong XJ. Exploration of Baihu Jia Renshen Decoction formula syndromes based on severe cases of critical care and integrative medicine and its clinical efficacy on clearing heat, elevating blood pressure, curing hypertonic and lowering blood sugar. *Zhongguo Zhong Yao Za Zhi*. 2019;44(18):3861–8. <https://doi.org/10.19540/j.cnki.cjcm.20190416.502> (Chinese).
 23. Chen H, Pan T, Liu P, Wang P, Xu S. Baihu Jia Guizhi decoction improves rheumatoid arthritis inflammation by regulating Succinate/SUCNR1 metabolic signaling pathway. *Evid Based Complement Alternat Med*. 2019;26(2019):3258572. <https://doi.org/10.1155/2019/3258572>.
 24. Gong HL, Tang WF, Wang J, Chen GY, Huang X. Effect of formula compatibility on the pharmacokinetics of components from Dachengqi Decoction [See Text] in rats. *Chin J Integr Med*. 2012;18(9):708–13. <https://doi.org/10.1007/s11655-012-1205-9> (Epub 2012 Aug 31).
 25. Liu G, Liu F, Xiao L, Kuang Q, He X, Wang Y, Wang Y. Narrative review of the mechanisms of action of dachengqi decoction in the treatment of hyperlipidemic pancreatitis on six-hollow-organs to be unblocked theory. *Ann Palliat Med*. 2020;9(4):2323–9. <https://doi.org/10.21037/apm-20-1332> (Epub 2020 Jul 20).
 26. Sun W, Chen Y, Li H, Liu H, Li J, Chen J, Feng D. Material basis and molecular mechanisms of Dachengqi decoction in the treatment of acute pancreatitis based on network pharmacology. *Biomed Pharmacother*. 2020;121: 109656. <https://doi.org/10.1016/j.biopha.2019.109656> (Epub 2019 Nov 23).
 27. Liu G, Liu F, Xiao L, Kuang Q, He X, Wang Y, Yu Y. Treatment of hyperlipidemic acute pancreatitis with modified Dachengqi decoction combining with conventional therapy based on “six-hollow-organs to be unblocked” theory. *Ann Palliat Med*. 2020;9(4):2045–53. <https://doi.org/10.21037/apm-20-1106> (Epub 2020 Jul 20).
 28. Ma S, Liu C, Li B, Zhang T, Jiang L, Wang R. Sonophoresis enhanced transdermal delivery of cisplatin in the xenografted tumor model of cervical cancer. *Oncol Targets Ther*. 2020;29(13):889–902. <https://doi.org/10.2147/OTT.S238126>.
 29. Pei L, Shen X, Yan Y, Tan C, Qu K, Zou J, Wang Y, Ping F. Virtual screening of the multi-pathway and multi-gene regulatory molecular mechanism of dachengqi decoction in the treatment of stroke based on network pharmacology. *Comb Chem High Throughput Screen*. 2020;23(8):775–87. <https://doi.org/10.2174/138620732366620031113747>.
 30. Zeng P, Wang XM, Su HF, Zhang T, Ning LN, Shi Y, Yang SS, Lin L, Tian Q. Protective effects of Da-cheng-qi decoction in rats with intracerebral hemorrhage. *Phytomedicine*. 2021;90: 153630. <https://doi.org/10.1016/j.phymed.2021.153630> (Epub 2021 Jun 17).
 31. Zhang KJ, Zhu JZ, Bao XY, Zheng Q, Zheng GQ, Wang Y. Shexiang baixin pills for coronary heart disease in animal models: preclinical evidence and promoting angiogenesis mechanism. *Front Pharmacol*. 2017;28(8):404. <https://doi.org/10.3389/fphar.2017.00404>.
 32. Stahl M, Tallman MS. Acute promyelocytic leukemia (APL): remaining challenges towards a cure for all. *Leuk Lymphoma*. 2019;60(13):3107–15. <https://doi.org/10.1080/10428194.2019.1613540> (Epub 2019 Dec 16).
 33. Mannan A, Muhsen IN, Barragán E, Sanz MA, Mohty M, Hashmi SK, Aljurf M. Genotypic and phenotypic characteristics of acute promyelocytic leukemia translocation variants. *Hematol Oncol Stem Cell Ther*. 2020;13(4):189–201. <https://doi.org/10.1016/j.hemonc.2020.05.007> (Epub 2020 May 20).
 34. Hai Y, Wang X, Song P, Li JY, Zhao LH, Xie F, Tan XM, Xie QJ, Yu L, Li Y, Wu ZR, Li HY. Realgar transforming solution-induced differentiation of NB4 cell by the degradation of PML/RAR α partially through the ubiquitin-proteasome pathway. *Arch Pharm Res*. 2019;42(8):684–94. <https://doi.org/10.1007/s12272-019-01170-9> (Epub 2019 Jun 18).
 35. Gurnari C, De Bellis E, Divona M, Ottone T, Lavorgna S, Voso MT. When poisons cure: the case of arsenic in acute promyelocytic leukemia. *Chemotherapy*. 2019;64(5–6):238–47. <https://doi.org/10.1159/000507805> (Epub 2020 Jun 10).
 36. Ablain J, Rice K, Soilili H, de Reynies A, Minucci S, de Thé H. Activation of a promyelocytic leukemia-tumor protein 53 axis underlies acute promyelocytic leukemia cure. *Nat Med*. 2014;20(2):167–74. <https://doi.org/10.1038/nm.3441> (Epub 2014 Jan 12).
 37. Korf K, Wodrich H, Haschke A, Ocampo C, Harder L, Gieseke F, Pollmann A, Dierck K, Prall S, Staeger H, Ma H, Horstmann MA, Evans RM, Sternsdorf T. The PML domain of PML-RAR α blocks senescence to promote leukemia. *Proc Natl Acad Sci USA*. 2014;111(33):12133–8. <https://doi.org/10.1073/pnas.1412944111> (Epub 2014 Aug 4).
 38. Cicconi L, Fenaux P, Kantarjian H, Tallman M, Sanz MA, Lo-Coco F. Molecular remission as a therapeutic objective in acute promyelocytic leukemia. *Leukemia*. 2018;32(8):1671–8. <https://doi.org/10.1038/s41375-018-0219-5> (Epub 2018 Jul 19).
 39. Fan J, He Q, Wang Z, Huang W, Cai Z. Self-assembled nanocomplex for co-delivery of arsenic-retinoic acid prodrug into acute promyelocytic leukemia cells. *J Biomed Nanotechnol*. 2018;14(6):1052–65. <https://doi.org/10.1166/jbn.2018.2556>.
 40. Zhang K, Lin H, Mao J, Luo X, Wei R, Su Z, Zhou B, Li D, Gao J, Shan H. An extracellular pH-driven targeted multifunctional manganese arsenite delivery system for tumor imaging and therapy. *Biomater Sci*. 2019;7(6):2480–90. <https://doi.org/10.1039/c9bm00216b>.
 41. Fan L, Liu C, Hu A, Liang J, Li F, Xiong Y, Mu CF. Dual oligopeptides modification mediates arsenic trioxide containing nanoparticles to eliminate primitive chronic myeloid leukemia cells inside bone marrow niches. *Int J Pharm*. 2020;579:119179. <https://doi.org/10.1016/j.ijpharm.2020.119179> (Epub 2020 Feb 26).
 42. Fang Y, Zhang Z. Arsenic trioxide as a novel anti-glioma drug: a review. *Cell Mol Biol Lett*. 2020;24(25):44. <https://doi.org/10.1186/s11658-020-00236-7>.
 43. Milano MT, Johnson MD, Sul J, Mohile NA, Korones DN, Okunieff P, Walter KA. Primary spinal cord glioma: a surveillance, epidemiology, and end results database study. *J Neurooncol*. 2010;98(1):83–92. <https://doi.org/10.1007/s11060-009-0054-7> (Epub 2009 Nov 7).
 44. Becker KP, Yu J. Status quo—standard-of-care medical and radiation therapy for glioblastoma. *Cancer J*. 2012;18(1):12–9. <https://doi.org/10.1097/PPO.0b013e318244d7eb>.
 45. Osuka S. Global trends in pre-clinical research on malignant glioma. *No Shinkei Geka*. 2021;49(3):485–9. <https://doi.org/10.1147/mf.1436204420> (Japanese).
 46. Ning S, Knox SJ. Optimization of combination therapy of arsenic trioxide and fractionated radiotherapy for malignant glioma. *Int J Radiat Oncol Biol Phys*. 2006;65(2):493–8. <https://doi.org/10.1016/j.ijrobp.2005.12.015> (Epub 2006 Mar 24).
 47. Sun Y, Wang C, Wang L, Dai Z, Yang K. Arsenic trioxide induces apoptosis and the formation of reactive oxygen species in rat glioma cells. *Cell Mol Biol Lett*. 2018;27(23):13. <https://doi.org/10.1186/s11658-018-0074-4>.
 48. Tao J, Fei W, Tang H, Li C, Mu C, Zheng H, Li F, Zhu Z. Angiopep-2-conjugated “Core-Shell” hybrid nanovehicles for targeted and pH-triggered delivery of arsenic trioxide into glioma. *Mol Pharm*. 2019;16(2):786–97. <https://doi.org/10.1021/acs.molpharmaceut.8b01056> (Epub 2019 Jan 24).
 49. Wang N, Zhang W, Hu D, Jiang L, Liu X, Tang S, Zhou X, Liu T, Tang X, Chai Y, Li M, Peng H, Du Z. Prodrug-Like[®] acetylmannosamine modified liposomes loaded with arsenic trioxide for the treatment of orthotopic glioma in mice. *J Pharm Sci*. 2020;109(9):2861–73. <https://doi.org/10.1016/j.xphs.2020.06.001> (Epub 2020 Jun 11).
 50. Linder B, Wehle A, Hehlhans S, Bonn F, Dikic I, Rödel F, Seifert V, Kögel D. Arsenic trioxide and (–)-gossypol synergistically target glioma stem-like cells via inhibition of hedgehog and notch signaling. *Cancers (Basel)*. 2019;11(3):350. <https://doi.org/10.3390/cancers11030350>.
 51. Lu Y, Han S, Zheng H, Ma R, Ping Y, Zou J, Tang H, Zhang Y, Xu X, Li F. A novel RGDyC/PEG co-modified PAMAM dendrimer-loaded arsenic trioxide of glioma targeting delivery system. *Int J Nanomed*. 2018;2(13):5937–52. <https://doi.org/10.2147/IJN.S175418>.

52. Shi X, Ma R, Lu Y, Cheng Y, Fan X, Zou J, Zheng H, Li F, Piao JG. iRGD and TGN co-modified PAMAM for multi-targeted delivery of ATO to gliomas. *Biochem Biophys Res Commun*. 2020;527(1):117–23. <https://doi.org/10.1016/j.bbrc.2020.04.064> (Epub 2020 Apr 28).
53. Hartke J, Johnson M, Ghabril M. The diagnosis and treatment of hepatocellular carcinoma. *Semin Diagn Pathol*. 2017;34(2):153–9. <https://doi.org/10.1053/j.semdp.2016.12.011> (Epub 2016 Dec 20).
54. Sim HW, Knox J. Hepatocellular carcinoma in the era of immunotherapy. *Curr Probl Cancer*. 2018;42(1):40–8. <https://doi.org/10.1016/j.currproblcancer.2017.10.007> (Epub 2017 Nov 15).
55. Jiang Y, Han Q, Zhao H, Zhang J. The mechanisms of HBV-induced hepatocellular carcinoma. *J Hepatocell Carcinoma*. 2021;20(8):435–50. <https://doi.org/10.2147/JHC.S307962>.
56. Kim SS, Lee S, Kim MJ. Prognostic factors of gadoxetic acid-enhanced MRI for postsurgical outcomes in multicentric hepatocellular carcinoma. *Eur Radiol*. 2021;31(5):3405–16. <https://doi.org/10.1007/s00330-020-07419-y> (Epub 2020 Nov 4).
57. Sadaf N, Kumar N, Ali M, Ali V, Bimal S, Haque R. Arsenic trioxide induces apoptosis and inhibits the growth of human liver cancer cells. *Life Sci*. 2018;15(205):9–17. <https://doi.org/10.1016/j.lfs.2018.05.006> (Epub 2018 May 5).
58. Swindell EP, Hankins PL, Chen H, Miodragović DU, O'Halloran TV. Anticancer activity of small-molecule and nanoparticulate arsenic(III) complexes. *Inorg Chem*. 2013;52(21):12292–304. <https://doi.org/10.1021/ic401211u> (Epub 2013 Oct 22).
59. Shoostary S, Behtash S, Nafisi S. Arsenic trioxide binding to serum proteins. *J Photochem Photobiol B*. 2015;148:31–6. <https://doi.org/10.1016/j.jphotobiol.2015.03.001> (Epub 2015 Apr 1).
60. Kong D, Jiang T, Liu J, Jiang X, Liu B, Lou C, Zhao B, Carroll SL, Feng G. Chemoembolizing hepatocellular carcinoma with microsphere cored with arsenic trioxide microcrystal. *Drug Deliv*. 2020;27(1):1729–40. <https://doi.org/10.1080/10717544.2020.1856219>.
61. Wu Q, Chen X, Wang P, Wu Q, Qi X, Han X, Chen L, Meng X, Xu K. Delivery of arsenic trioxide by multifunction nanoparticles to improve the treatment of hepatocellular carcinoma. *ACS Appl Mater Interfaces*. 2020;12(7):8016–29. <https://doi.org/10.1021/acsami.9b22802> (Epub 2020 Feb 10).
62. Eslahi M, Dana PM, Asemi Z, Hallajzadeh J, Mansournia MA, Yousefi B. The effects of chitosan-based materials on glioma: Recent advances in its applications for diagnosis and treatment. *Int J Biol Macromol*. 2021;31(168):124–9. <https://doi.org/10.1016/j.jbiomac.2020.11.180> (Epub 2020 Dec 1).
63. Chi X, Zhang R, Zhao T, Gong X, Wei R, Yin Z, Lin H, Li D, Shan H, Gao J. Targeted arsenite-loaded magnetic multifunctional nanoparticles for treatment of hepatocellular carcinoma. *Nanotechnology*. 2019;30(17):175101. <https://doi.org/10.1088/1361-6528/aaff9e> (Epub 2019 Jan 17).
64. Akhtar A, Ghali L, Wang SX, Bell C, Li D, Wen X. Optimisation of folate-mediated liposomal encapsulated arsenic trioxide for treating HPV-positive cervical cancer cells in vitro. *Int J Mol Sci*. 2019;20(9):2156. <https://doi.org/10.3390/ijms20092156>.
65. Zhang L, Zhou Y, Kong J, Zhang L, Yuan M, Xian S, Wang Y, Cheng Y, Yang X. Effect of arsenic trioxide on cervical cancer and its mechanisms. *Exp Ther Med*. 2020;20(6):169. <https://doi.org/10.3892/etm.2020.9299> (Epub 2020 Oct 9).
66. Akhtar A, Wang SX, Ghali L, Bell C, Wen X. Effective delivery of arsenic trioxide to HPV-positive cervical cancer cells using optimised liposomes: a size and charge study. *Int J Mol Sci*. 2018;19(4):1081. <https://doi.org/10.3390/ijms19041081>.
67. Wang X, Li D, Ghali L, Xia R, Munoz LP, Garelick H, Bell C, Wen X. Therapeutic potential of delivering arsenic trioxide into HPV-infected cervical cancer cells using liposomal nanotechnology. *Nanoscale Res Lett*. 2016;11(1):94. <https://doi.org/10.1186/s11671-016-1307-y> (Epub 2016 Feb 18).
68. Qian C, Wang Y, Chen Y, Zeng L, Zhang Q, Shuai X, Huang K. Suppression of pancreatic tumor growth by targeted arsenic delivery with anti-CD44v6 single chain antibody conjugated nanoparticles. *Biomaterials*. 2013;34(26):6175–84. <https://doi.org/10.1016/j.biomaterials.2013.04.056> (Epub 2013 May 27).
69. Hajipour H, Hamishehkar H, Nazari Soltan Ahmad S, Barghi S, Maroufi NF, Taheri RA. Improved anticancer effects of epigallocatechin gallate using RGD-containing nanostructured lipid carriers. *Artif Cells Nanomed Biotechnol*. 2018;46(Suppl 1):283–92. <https://doi.org/10.1080/21691401.2017.1423493> (Epub 2018 Jan 8).
70. Fang W, Peng ZL, Dai YJ, Wang DL, Huang P, Huang HP. (–)-Epigallocatechin-3-gallate encapsulated realgar nanoparticles exhibit enhanced anticancer therapeutic efficacy against acute promyelocytic leukemia. *Drug Deliv*. 2019;26(1):1058–67. <https://doi.org/10.1080/10717544.2019.1672830>.
71. Huang X, Lin C, Luo C, Guo Y, Li J, Wang Y, Xu J, Zhang Y, Wang H, Liu Z, Chen B. Fe₃O₄@M nanoparticles for MRI-targeted detection in the early lesions of atherosclerosis. *Nanomedicine*. 2021;33: 102348. <https://doi.org/10.1016/j.nano.2020.102348> (Epub 2020 Dec 13).
72. Jin Q, Liu J, Zhu W, Dong Z, Liu Z, Cheng L. Albumin-assisted synthesis of ultrasmall Fe₂S₃ nanodots for imaging-guided photothermal enhanced photodynamic therapy. *ACS Appl Mater Interfaces*. 2018;10(1):332–40. <https://doi.org/10.1021/acsami.7b16890> (Epub 2017 Dec 19).
73. Fei W, Li C, Tao J, Cai X, Yao W, Ye Y, Zhang Y, Yao Y, Song Q, Li F, Zheng C. Construction of arsenic-metal complexes loaded nanodrugs for solid tumor therapy: a mini review. *Int J Pharm*. 2020;583:119385. <https://doi.org/10.1016/j.ijpharm.2020.119385> (Epub 2020 May 4).
74. El-Boubbou K. Magnetic iron oxide nanoparticles as drug carriers: clinical relevance. *Nanomedicine (Lond)*. 2018;13(8):953–71. <https://doi.org/10.2217/nmm-2017-0336> (Epub 2018 Jan 29).
75. El-Boubbou K. Magnetic iron oxide nanoparticles as drug carriers: preparation, conjugation and delivery. *Nanomedicine (Lond)*. 2018;13(8):929–52. <https://doi.org/10.2217/nmm-2017-0320> (Epub 2018 Mar 16).
76. Kim DH, Guo Y, Zhang Z, Procissi D, Nicolai J, Omary RA, Larson AC. Temperature-sensitive magnetic drug carriers for concurrent gemcitabine chemohyperthermia. *Adv Healthc Mater*. 2014;3(5):714–24. <https://doi.org/10.1002/adhm.201300209> (Epub 2013 Oct 21).
77. Gholami A, Mousavi SM, Hashemi SA, Ghasemi Y, Chiang WH, Parvin N. Current trends in chemical modifications of magnetic nanoparticles for targeted drug delivery in cancer chemotherapy. *Drug Metab Rev*. 2020;52(1):205–24. <https://doi.org/10.1080/03602532.2020.1726943> (Epub 2020 Feb 21).
78. Lee GY, Qian WP, Wang L, Wang YA, Staley CA, Satpathy M, Nie S, Mao H, Yang L. Theranostic nanoparticles with controlled release of gemcitabine for targeted therapy and MRI of pancreatic cancer. *ACS Nano*. 2013;7(3):2078–89. <https://doi.org/10.1021/nm3043463> (Epub 2013 Mar 12).
79. Yang R, An Y, Miao F, Li M, Liu P, Tang Q. Preparation of folic acid-conjugated, doxorubicin-loaded, magnetic bovine serum albumin nanoparticles and their antitumor effects in vitro and in vivo. *Int J Nanomed*. 2014;4(9):4231–43. <https://doi.org/10.2147/IJN.S67210>.
80. Lee J, Kim H, Kim S, Lee H, Kim J, Kim N, et al. A multifunctional mesoporous nanocontainer with an iron oxide core and a cyclodextrin gatekeeper for an efficient theranostic platform. *J Mater Chem*. 2012;22(28):14061–7.
81. Choi GE, Kang MS, Kim YJ, Yoon JJ, Jeong YI. Magnetically responsive drug delivery using doxorubicin and iron oxide nanoparticle-incorporated lipocomplexes. *J Nanosci Nanotechnol*. 2019;19(2):675–9. <https://doi.org/10.1166/jnn.2019.15910>.
82. Ketkar-Atre A, Struys T, Dresselaers T, Hoenius M, Mannaerts I, Ni Y, Lambrechts I, Van Grunsven LA, De Cuyper M, Himmelreich U. In vivo hepatocyte MR imaging using lactose functionalized magnetoliposomes. *Biomaterials*. 2014;35(3):1015–24. <https://doi.org/10.1016/j.biomaterials.2013.10.029> (Epub 2013 Nov 5).
83. Soenen SJ, Velde GV, Ketkar-Atre A, Himmelreich U, De Cuyper M. Magnetoliposomes as magnetic resonance imaging contrast agents. *Wiley Interdiscip Rev Nanomed Nanobiotechnol*. 2011;3(2):197–211. <https://doi.org/10.1002/wnan.122>.
84. Millart E, Lesieur S, Faivre V. Superparamagnetic lipid-based hybrid nanosystems for drug delivery. *Expert Opin Drug Deliv*. 2018;15(5):523–40. <https://doi.org/10.1080/17425247.2018.1453804> (Epub 2018 Mar 29).
85. Li B, Li B, He D, Feng C, Luo Z, He M. Preparation, characterization, and in vitro pH-sensitivity evaluation of superparamagnetic iron oxide nanoparticle- misonidazole pH-sensitive liposomes. *Curr Drug Deliv*.

- 2019;16(3):254–67. <https://doi.org/10.2174/1567201816666181114124333>.
86. Zhu C, Yang H, Shen L, Zheng Z, Zhao S, Li Q, Yu F, Cen L. Microfluidic preparation of PLGA microspheres as cell carriers with sustainable Rapa release. *J Biomater Sci Polym Ed.* 2019;30(9):737–55. <https://doi.org/10.1080/09205063.2019.1602930> (Epub 2019 Apr 19).
 87. Ramazani F, Chen W, van Nostrum CF, Storm G, Kiessling F, Lammers T, Hennink WE, Kok RJ. Strategies for encapsulation of small hydrophilic and amphiphilic drugs in PLGA microspheres: state-of-the-art and challenges. *Int J Pharm.* 2016;499(1–2):358–67. <https://doi.org/10.1016/j.ijpharm.2016.01.020> (Epub 2016 Jan 12).
 88. Wei Y, Wu Y, Wen K, Bazybek N, Ma G. Recent research and development of local anesthetic-loaded microspheres. *J Mater Chem B.* 2020;8(30):6322–32. <https://doi.org/10.1039/d0tb01129k>.
 89. Ayyanaar S, Kesavan MP, Balachandran C, Rasala S, Rameshkumar P, Aoki S, Rajesh J, Webster TJ, Rajagopal G. Iron oxide nanoparticle core-shell magnetic microspheres: applications toward targeted drug delivery. *Nanomedicine.* 2020;24: 102134. <https://doi.org/10.1016/j.nano.2019.102134> (Epub 2019 Dec 10).
 90. Poorgholy N, Massoumi B, Ghorbani M, Jaymand M, Hamishehkar H. Intelligent anticancer drug delivery performances of two poly(*N*-isopropylacrylamide)-based magnetite nanohydrogels. *Drug Dev Ind Pharm.* 2018;44(8):1254–61. <https://doi.org/10.1080/03639045.2018.1442845> (Epub 2018 Feb 27).
 91. Zhao Y, Onda K, Yuan B, Tanaka S, Kiyomi A, Sugiyama K, Sugiura M, Takagi N, Hirano T. Arsenic disulfide-induced apoptosis and its potential mechanism in two- and three-dimensionally cultured human breast cancer MCF-7 cells. *Int J Oncol.* 2018;52(6):1959–71. <https://doi.org/10.3892/ijo.2018.4357> (Epub 2018 Apr 4).
 92. Mody KT, Popat A, Mahony D, Cavallaro AS, Yu C, Mitter N. Mesoporous silica nanoparticles as antigen carriers and adjuvants for vaccine delivery. *Nanoscale.* 2013;5(12):5167–79. <https://doi.org/10.1039/c3nr00357d>.
 93. Manshadi MKD, Saadat M, Mohammadi M, Kamali R, Shamsi M, Naseh M, Sanati-Nezhad A. Magnetic aerosol drug targeting in lung cancer therapy using permanent magnet. *Drug Deliv.* 2019;26(1):120–8. <https://doi.org/10.1080/10717544.2018.1561765>.
 94. Lvov YM, Shchukin DG, Möhwald H, Price RR. Halloysite clay nanotubes for controlled release of protective agents. *ACS Nano.* 2008;2(5):814–20. <https://doi.org/10.1021/nl800259q>.
 95. Abdullayev E, Lvov Y. Halloysite clay nanotubes for controlled release of protective agents. *J Nanosci Nanotechnol.* 2011;11(11):10007–26. <https://doi.org/10.1166/jnn.2011.5724>.
 96. Vergaro V, Lvov YM, Leporatti S. Halloysite clay nanotubes for resveratrol delivery to cancer cells. *Macromol Biosci.* 2012;12(9):1265–71. <https://doi.org/10.1002/mabi.201200121> (Epub 2012 Aug 8).
 97. Lisuzzo L, Cavallaro G, Milioto S, Lazzara G. Halloysite nanotubes coated by chitosan for the controlled release of khellin. *Polymers (Basel).* 2020;12(8):1766. <https://doi.org/10.3390/polym12081766>.
 98. Homayun B, Choi HJ. Halloysite nanotube-embedded microparticles for intestine-targeted co-delivery of biopharmaceuticals. *Int J Pharm.* 2020;579:119152. <https://doi.org/10.1016/j.ijpharm.2020.119152> (Epub 2020 Feb 17).
 99. Neupane R, Boddhu SHS, Abou-Dahech MS, Bachu RD, Terrero D, Babu RJ, Tiwari AK. Transdermal delivery of chemotherapeutics: strategies, requirements, and opportunities. *Pharmaceutics.* 2021;13(7):960. <https://doi.org/10.3390/pharmaceutics13070960>.
 100. Ma X, Jin T, Han C, Shi N, Liang G, Wen Y, Yang J, Fu X, Lan T, Jiang K, Nunes QM, Chvanov M, Criddle DN, Philips AR, Deng L, Liu T, Windsor JA, Sutton R, Du D, Huang W, Xia Q. Aqueous extraction from dachengqi formula granules reduces the severity of mouse acute pancreatitis via inhibition of pancreatic pro-inflammatory signalling pathways. *J Ethnopharmacol.* 2020;257:112861. <https://doi.org/10.1016/j.jep.2020.112861> (Epub 2020 Apr 18).
 101. Atlan M, Neman J. Targeted transdermal delivery of curcumin for breast cancer prevention. *Int J Environ Res Public Health.* 2019;16(24):4949. <https://doi.org/10.3390/ijerph16244949>.
 102. Lin YL, Chen CH, Wu HY, Tsai NM, Jian TY, Chang YC, Lin CH, Wu CH, Hsu FT, Leung TK, Liao KW. Inhibition of breast cancer with transdermal tamoxifen-encapsulated lipoplex. *J Nanobiotechnol.* 2016;19(14):11. <https://doi.org/10.1186/s12951-016-0163-3>.
 103. Lee O, Ivancic D, Allu S, Shidfar A, Kenney K, Helenowski I, Sullivan ME, Muzzio M, Scholtens D, Chatterton RT Jr, Bethke KP, Hansen NM, Khan SA. Local transdermal therapy to the breast for breast cancer prevention and DCIS therapy: preclinical and clinical evaluation. *Cancer Chemother Pharmacol.* 2015;76(6):1235–46. <https://doi.org/10.1007/s00280-015-2848-y>.
 104. Toyoda M, Hama S, Ikeda Y, Nagasaki Y, Kogure K. Anti-cancer vaccination by transdermal delivery of antigen peptide-loaded nanogels via iontophoresis. *Int J Pharm.* 2015;483(1–2):110–4. <https://doi.org/10.1016/j.ijpharm.2015.02.024> (Epub 2015 Feb 11).
 105. Zhao Y, Onda K, Sugiyama K, Yuan B, Tanaka S, Takagi N, Hirano T. [Corrigendum] Antitumor effects of arsenic disulfide on the viability, migratory ability, apoptosis and autophagy of breast cancer cells. *Oncol Rep.* 2020;44(3):1293. <https://doi.org/10.3892/or.2020.7653> (Epub 2020 Jun 19. Erratum for: *Oncol Rep.* 2019 Jan;41(1):27–42).
 106. Xiaoxia X, Jing S, Dongbin X, Yonggang T, Jingke Z, Yanying Z, Hulai W. Realgar nanoparticles inhibit migration, invasion and metastasis in a mouse model of breast cancer by suppressing matrix metalloproteinases and angiogenesis. *Curr Drug Deliv.* 2020;17(2):148–58. <https://doi.org/10.2174/1567201817666200115105633>.
 107. Zhao QH, Zhang Y, Liu Y, Wang HL, Shen YY, Yang WJ, Wen LP. Anticancer effect of realgar nanoparticles on mouse melanoma skin cancer in vivo via transdermal drug delivery. *Med Oncol.* 2010;27(2):203–12. <https://doi.org/10.1007/s12032-009-9192-1> (Epub 2009 Mar 12).
 108. Zhao WL, Yi Z, Huang QW, Zhou JL, Chen SL. Research on revision of origins to Chinese medicinal materials in 2020 edition of Chinese pharmacopoeia. *Zhongguo Zhong Yao Za Zhi.* 2021;46(10):2617–22. <https://doi.org/10.19540/j.cnki.cjcm.20210226.104> (Chinese).
 109. Liu J, Wei LX, Wang Q, Lu YF, Zhang F, Shi JZ, Li C, Cherian MG. A review of cinnabar (HgS) and/or realgar (As₄S₄)-containing traditional medicines. *J Ethnopharmacol.* 2018;10(210):340–50. <https://doi.org/10.1016/j.jep.2017.08.037> (Epub 2017 Aug 31).
 110. Lu YF, Yan JW, Wu Q, Shi JZ, Liu J, Shi JS. Realgar- and cinnabar-containing an-gong-niu-huang wan (AGNH) is much less acutely toxic than sodium arsenite and mercuric chloride. *Chem Biol Interact.* 2011;189(1–2):134–40. <https://doi.org/10.1016/j.cbi.2010.11.006> (Epub 2010 Nov 19).
 111. Li A, Zhang JY, Xiao X, Wang SS, Wan JB, Chai YS, Li P, Wang YT. Hepatorenal protective effects of medicinal herbs in An-Gong-Niu-Huang Wan (AGNH) against cinnabar- and realgar-induced oxidative stress and inflammatory damage in mice. *Food Chem Toxicol.* 2018;119:445–56. <https://doi.org/10.1016/j.fct.2017.11.054> (Epub 2017 Dec 2).
 112. Lv L, Zheng J, Zhang Y, Chen B, Yan F, Qin X, Zheng C, Wu Z, Feng K. Respiratory nursing care with Angong Niuhuang pill for patients with chronic obstructive pulmonary disease following cardiac surgery. *Jpn J Nurs Sci.* 2021;18(1):e12344. <https://doi.org/10.1111/jjns.12344> (Epub 2020 Sep 13).
 113. Chai Y, Yin Z, Fan Q, Zhang Z, Ye K, Xu Y, Xiao W, Chai X, Zhu T, Nie H. Protective effects of angong niuhuang pill on early atherosclerosis in ApoE^{−/−} mice by reducing the inflammatory response. *Evid Based Complement Alternat Med.* 2019;20(2019):9747212. <https://doi.org/10.1155/2019/9747212>.
 114. Yang M, Wang L, Zhang T, Zhu A, Sun Y, Zhao J, Liu D, Wang Q, Zeng K. Different proteomic profiles of cinnabar upon therapeutic and toxic exposure reveal distinctive biological manifestations. *J Ethnopharmacol.* 2020;10(253):112668. <https://doi.org/10.1016/j.jep.2020.112668> (Epub 2020 Feb 14).
 115. Tsoi B, Wang S, Gao C, Luo Y, Li W, Yang D, Yang D, Shen J. Realgar and cinnabar are essential components contributing to neuroprotection of Angong Niuhuang Wan with no hepatorenal toxicity in transient ischemic brain injury. *Toxicol Appl Pharmacol.* 2019;377:114613. <https://doi.org/10.1016/j.taap.2019.114613> (Epub 2019 Jun 14).
 116. Chen C, Zhang BB, Hu AL, Li H, Liu J, Zhang F. Protective role of cinnabar and realgar in Hua-Feng-Dan against LPS plus rotenone-induced neurotoxicity and disturbance of gut microbiota in rats. *J Ethnopharmacol.* 2020;247:112299. <https://doi.org/10.1016/j.jep.2019.112299> (Epub 2019 Oct 10).
 117. Wang Y, Zhou S, Ma H, Shi JS, Lu YF. Investigation of the differential transport mechanism of cinnabar and mercury containing compounds. *Environ Toxicol Pharmacol.* 2019;66:83–90. <https://doi.org/10.1016/j.etap.2018.12.020> (Epub 2018 Dec 26).

118. Lu YT, Qi WZ, Wang S, Song XN, Yang DY, Song M, Hang TJ. Toxicity and risk assessment of mercury exposures from cinnabar and Baizi Yangxin Pills based on pharmacokinetic and tissue distribution studies. *J Ethnopharmacol*. 2020;250:112489. <https://doi.org/10.1016/j.jep.2019.112489> (Epub 2019 Dec 19).
119. Liu D, Li J, Wang C, An L, Lin J, Tian Q, Yang S. Ultrasmall Fe@Fe₃O₄ nanoparticles as T1–T2 dual-mode MRI contrast agents for targeted tumor imaging. *Nanomedicine*. 2021;32:102335. <https://doi.org/10.1016/j.nano.2020.102335> (Epub 2020 Nov 19).
120. Zhang L, Liu L, Zhan S, Chen L, Wang Y, Zhang Y, Du J, Wu Y, Gu L. Arsenic trioxide suppressed migration and angiogenesis by targeting FOXO3a in gastric cancer cells. *Int J Mol Sci*. 2018;19(12):3739. <https://doi.org/10.3390/ijms19123739>.
121. Kim SH, Yoo HS, Joo MK, Kim T, Park JJ, Lee BJ, Chun HJ, Lee SW, Bak YT. Arsenic trioxide attenuates STAT-3 activity and epithelial-mesenchymal transition through induction of SHP-1 in gastric cancer cells. *BMC Cancer*. 2018;18(1):150. <https://doi.org/10.1186/s12885-018-4071-9>.
122. Zhang F, Duan J, Song H, Yang L, Zhou M, Wang X. Combination of canstatin and arsenic trioxide suppresses the development of hepatocellular carcinoma. *Drug Dev Res*. 2021;82(3):430–9. <https://doi.org/10.1002/ddr.21766> (Epub 2020 Nov 27).
123. Wang G, Zhang T, Sun W, Wang H, Yin F, Wang Z, Zuo D, Sun M, Zhou Z, Lin B, Xu J, Hua Y, Li H, Cai Z. Arsenic sulfide induces apoptosis and autophagy through the activation of ROS/JNK and suppression of Akt/mTOR signaling pathways in osteosarcoma. *Free Radic Biol Med*. 2017;106:24–37. <https://doi.org/10.1016/j.freeradbiomed.2017.02.015> (Epub 2017 Feb 7).
124. Zhao Y, Zhao X, Cheng Y, Guo X, Yuan W. Iron oxide nanoparticles-based vaccine delivery for cancer treatment. *Mol Pharm*. 2018;15(5):1791–9. <https://doi.org/10.1021/acs.molpharmaceut.7b01103> (Epub 2018 Mar 23).
125. Zhang Y, Shen L, Wang P, Xi W, Yu Z, Huang X, Wang X, Shou D. Treatment with vancomycin loaded calcium sulphate and autogenous bone in an improved rabbit model of bone infection. *J Vis Exp*. 2019;(145). <https://doi.org/10.3791/57294>
126. He Q, Ma J, Kalavagunta PK, Zhou L, Zhu J, Dong J, Ahmad O, Du Y, Wei L, Shang J. HgS inhibits oxidative stress caused by hypoxia through regulation of 5-HT metabolism pathway. *Int J Mol Sci*. 2019;20(6):1364. <https://doi.org/10.3390/ijms20061364>.
127. Kaplan A, Kutlu HM, Ciftci GA. Fe₃O₄ nanoparticles: genomic and apoptotic evaluations on A549 lung adenocarcinoma cell line. *Nutr Cancer*. 2020;72(4):708–21. <https://doi.org/10.1080/01635581.2019.1643031> (Epub 2019 Jul 23).
128. Yan L, Liu X, Liu WX, Tan XQ, Xiong F, Gu N, Hao W, Gao X, Cao JM. Fe₂O₃ nanoparticles suppress Kv1.3 channels via affecting the redox activity of Kvβ2 subunit in Jurkat T cells. *Nanotechnology*. 2015;26(50):505103. <https://doi.org/10.1088/0957-4484/26/50/505103> (Epub 2015 Nov 20).
129. Ikarashi N, Ogiue N, Toyoda E, Kon R, Ishii M, Toda T, Aburada T, Ochiai W, Sugiyama K. Gypsum fibrosum and its major component CaSO₄ increase cutaneous aquaporin-3 expression levels. *J Ethnopharmacol*. 2012;139(2):409–13. <https://doi.org/10.1016/j.jep.2011.11.025> (Epub 2011 Nov 25).
130. Zhang Z, Zhang F, Zhang H. In vitro response of immune cells on metal oxide nanoparticles with different solubility. *J Nanosci Nanotechnol*. 2016;16(6):5546–52. <https://doi.org/10.1166/jnn.2016.11751>.
131. Rajiv S, Jerobin J, Saranya V, Nainawat M, Sharma A, Makwana P, Gayathri C, Bharath L, Singh M, Kumar M, Mukherjee A, Chandrasekaran N. Comparative cytotoxicity and genotoxicity of cobalt (II, III) oxide, iron (III) oxide, silicon dioxide, and aluminum oxide nanoparticles on human lymphocytes in vitro. *Hum Exp Toxicol*. 2016;35(2):170–83. <https://doi.org/10.1177/0960327115579208> (Epub 2015 Mar 31).
132. Li X, Liu YF, Xiang XR, Zhou YB, Zhang ZL. Comparative study of the effects of gypsum fibrosum and gypsum fibrosum preparatum in promoting granulation. *Zhong Xi Yi Jie He Xue Bao*. 2006;4(6):624–7. <https://doi.org/10.3736/jcim20060617> (Chinese).
133. Han Z, Song L, Qi K, Ding Y, Wei M, Jia Y. Deciphering the key pharmacological pathways and targets of yisui qinghuang powder that acts on myelodysplastic syndromes using a network pharmacology-based strategy. *Evid Based Complement Alternat Med*. 2020;8(2020):8877295. <https://doi.org/10.1155/2020/8877295>.
134. Gong J, Zheng S, Zhang L, Wang Y, Meng J. Induction of K562 Cell apoptosis by As4S4 via down-regulating miR181. *Med Sci Monit*. 2017;10(23):144–50. <https://doi.org/10.12659/msm.899214>.
135. Song X, You J, Shao H, Yan C. Effects of surface modification of As₂O₃-loaded PLGA nanoparticles on its anti-liver cancer ability: an in vitro and in vivo study. *Colloids Surf B Biointerfaces*. 2018;1(169):289–97. <https://doi.org/10.1016/j.colsurfb.2018.05.024> (Epub 2018 May 21).
136. Song P, Chen P, Wang D, Wu Z, Gao Q, Wang A, Zhu R, Wang Y, Wang X, Zhao L, Duan Z, Zhu S, Cui P, Li Y, Li H. Realgar transforming solution displays anticancer potential against human hepatocellular carcinoma HepG2 cells by inducing ROS. *Int J Oncol*. 2017;50(2):660–70. <https://doi.org/10.3892/ijo.2016.3831> (Epub 2016 Dec 30).
137. Qin YU, Wang H, Liu ZY, Liu J, Wu JZ. Realgar quantum dots induce apoptosis and necrosis in HepG2 cells through endoplasmic reticulum stress. *Biomed Rep*. 2015;3(5):657–62. <https://doi.org/10.3892/br.2015.489> (Epub 2015 Jul 15).
138. Cao H, Feng Y, Chen L. Repression of MicroRNA-372 by arsenic sulphide inhibits prostate cancer cell proliferation and migration through regulation of large tumour suppressor kinase 2. *Basic Clin Pharmacol Toxicol*. 2017;120(3):256–63. <https://doi.org/10.1111/bcpt.12687> (Epub 2016 Dec 28).
139. Zhang X, Kang T, Zhang L, Tong Y, Ding W, Chen S. NFATc3 mediates the sensitivity of gastric cancer cells to arsenic sulfide. *Oncotarget*. 2017;8(32):52735–45. <https://doi.org/10.18632/oncotarget.17175>.
140. Tan Z, Zhang X, Kang T, Zhang L, Chen S. Arsenic sulfide amplifies JQ1 toxicity via mitochondrial pathway in gastric and colon cancer cells. *Drug Des Devel Ther*. 2018;14(12):3913–27. <https://doi.org/10.2147/DDDT.S180976>.
141. Zhao Y, Yuan B, Onda K, Sugiyama K, Tanaka S, Takagi N, Hirano T. Anti-cancer efficacies of arsenic disulfide through apoptosis induction, cell cycle arrest, and pro-survival signal inhibition in human breast cancer cells. *Am J Cancer Res*. 2018;8(3):366–86.
142. Yousefi B, Semnani V, Mokhtari T, Zarbakhsh S, Amjad MHT, Barati M, Doustmohammadi H. Co-administration of aluminum sulfate and propolis regulates matrix metalloproteinases-2/9 expression and improves the uterine leiomyoma in adult rat model. *Biol Trace Elem Res*. 2021;199(3):1002–12. <https://doi.org/10.1007/s12011-020-02200-0> (Epub 2020 Jun 27).
143. Pan W, Cai S, Latour JM, Zhong M, Lv M, Li J, Zhang X, Zhang Y. External use of Mirabilite combined with Lactulose improves postoperative gastrointestinal mobility among older patients undergoing abdominal surgery. *J Adv Nurs*. 2021;77(2):755–62. <https://doi.org/10.1111/jan.14640> (Epub 2020 Nov 24).
144. Chang CJ, Yang YH, Chen PC, Peng HY, Lu YC, Song SR, Yang HY. Stomach cancer and exposure to talc powder without asbestos via Chinese herbal medicine: a population-based cohort study. *Int J Environ Res Public Health*. 2019;16(5):717. <https://doi.org/10.3390/ijerph16050717>.

Publisher's Note

Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

Ready to submit your research? Choose BMC and benefit from:

- fast, convenient online submission
- thorough peer review by experienced researchers in your field
- rapid publication on acceptance
- support for research data, including large and complex data types
- gold Open Access which fosters wider collaboration and increased citations
- maximum visibility for your research: over 100M website views per year

At BMC, research is always in progress.

Learn more biomedcentral.com/submissions

